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# Clinical Disease Progression in Parkinson's Disease

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The Norwegian  
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Disorders

The Norwegian Centre for Movement Disorders

Stavanger University Hospital

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**To Vanja, Sofia and Clara**

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## Research environment

The present study was conducted during the years 2002 to 2006 at the Department of Neurology and the Norwegian Centre for Movement Disorders, Stavanger University Hospital, Norway.

Parkinson's disease is a rapidly developing scientific area in which research is increasingly based on collaboration between professional milieus, both in national and international perspective. In addition to staff at the Department of Neurology and the Norwegian Centre for Movement Disorders, Stavanger University Hospital, the following persons and groups have been involved in the Stavanger Parkinson project and directly or indirectly contributed to papers included in this thesis:

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## List of publications

### Paper 1:

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### Paper 3:

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# 1. Introduction

## 1.1 General introduction and history of PD

Parkinson's disease (PD) is generally defined as a chronic progressive neurodegenerative disorder neuropathologically characterized by nigrostriatal cell loss and presence of intracellular inclusions called Lewy bodies, leading to the four clinical cardinal signs tremor, rigidity, bradykinesia, and postural instability.

The clinical definition of PD is thus similar to the description given by the famous physician James Parkinson in his "An essay on a shaking palsy" published in 1817. Based on the observation of people in the streets of London and some of his own patients, he was the first to describe "involuntary tremulous motion", a "propensity to bend forwards", and "to pass from a walking to a running pace" as distinctive features of the disease.<sup>1</sup> Jean-Martin Charcot then, more than half a century later, also distinguished the hallmark of rigidity in his teaching lectures at the Salpêtrière Hospital and honored James Parkinson's work by giving the disease his name.<sup>2</sup>

Since then PD has been the subject of comprehensive research, reaching a landmark in 1953 when cell loss in the substantia nigra was found in patients with parkinsonism, and in the 1960s when depletion of the neurotransmitter dopamine could be related to the disease.<sup>3,4</sup> Subsequently, a further milestone in the history of PD was reached by the discovery that levodopa, a precursor of dopamine that passes the blood-brain barrier, improves parkinsonian symptoms.<sup>5</sup> Although a wide range of differently acting agents has been developed since, levodopa is still considered to be the most effective drug therapy in PD.<sup>6</sup>

Also surgical intervention has a long tradition in PD, but played a minor role until stereotactic surgery with chronic stimulation of specific brainstem and midbrain nuclei was developed and became established during the 1990s.<sup>7</sup> Surgical treatment

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of PD is, however, still limited to a rather small subgroup of patients with fluctuating motor symptoms or disabling tremor.

In the last decade, PD has increasingly been recognized as a disorder that not only causes typical motor symptoms, but also a wide range of non-motor problems, leading to disability and diminishing quality of life in patients and caregivers.<sup>8</sup> The fact that most of these symptoms do not respond to dopaminergic treatment indicates that also other neurotransmitter systems become involved during the course of the disease. There is now increasingly more evidence that PD develops from a restricted dopamine-deficit disease to a multisystem brain disorder.<sup>9</sup>

In 1997, a new area in PD research was obtained when mutations in the gene coding for  $\alpha$ -synuclein could be linked to familial parkinsonism.<sup>10</sup> This led to the pivotal discovery that  $\alpha$ -synuclein is the major component of Lewy bodies.<sup>11</sup> Later on, mutations in several gene loci were shown to be related to inherited PD.<sup>12</sup> Although such aberrant genes have been found only in a rather small number of PD patients, these findings confirmed the long-lasting hypothesis that genetic susceptibility does play a role in the etiology of the disease. They also gave new insights into the molecular pathogenesis of PD in which mitochondrial dysfunction and impairment of the ubiquitin-proteasome system seem to be of crucial relevance.<sup>13</sup>

Despite the recent advances in the field of PD, evidence-based knowledge about the progression of the disease is still limited. Due to a lack of in-vivo biomarkers and the current limitations of neuroimaging methods to adequately measure non-dopaminergic involvement in PD, clinical assessment using established clinical rating scales remains the gold standard in charting the course of the disease.<sup>14</sup> A drawback of many clinical studies is, however, that they are based on short-term investigations and selected patient cohorts. Due to the slowly progressive nature and the heterogeneity of the disease, prospective longitudinal studies following representative patient cohorts over several years are expected to provide the most valid information on the progression of PD.

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Charting the clinical course of PD is important for several reasons: Valid information about motor and non-motor decline and associated risk-factors is valuable in anticipating the needs of patients and caregivers and in estimating socio-economic costs. Furthermore, it is helpful to design and evaluate the results of epidemiological and clinical studies and may have implications for the understanding of underlying pathological changes.

In the present thesis, different aspects of clinical disease progression in PD are presented, based on results from four prospective longitudinal investigations, all using a population-based cohort of patients with PD.

## 1.2 Epidemiology of PD

Besides essential tremor, PD is the most common neurodegenerative movement disorder,<sup>15</sup> affecting about 100 to 150 people of 100.000 inhabitants in population-based studies in Western and Northern European countries.<sup>16</sup> The estimated worldwide prevalence rate is four million people, with the disease found in all ethnic groups, but with geographical differences in prevalence. Annual incidence rates of PD in population-based studies in European countries and the USA vary somewhat, reporting an age-adjusted crude incidence in between 8.6 and 19.0/100.000 inhabitants.<sup>17</sup> Gender distribution is almost equal, although some studies indicate a slight male preponderance.<sup>17</sup> As it is mainly an illness of later life and most frequently seen after the age of 50 years, it is more common in developed countries where people live longer. Approximately 1-2% of the population over 65 years suffers from PD, increasing to 3% to 5% in people 85 years and older.<sup>18</sup> Early onset of the disease is, however, possible, with about 4% of the patients developing clinical signs of the disease before an age of 50 years.<sup>19</sup>

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## 1.3 Etiology of PD

The cause of PD is unclear in the very majority of cases. Previously understood as a single entity, clinical studies indicate heterogeneity of PD and increasing evidence suggests that the disease may represent different conditions terminating in a common pathway.<sup>20</sup>

Due to aggregation of PD within families and pedigrees, a genetic cause of the disease has been hypothesized for several decades. In several epidemiological studies, family members of affected patients were shown to have a 3- to 4-fold increased risk of developing the disease compared to subjects in the general population or controls.<sup>21, 22</sup> A breakthrough in the genetics of PD was the discovery of a mutation in the  *$\alpha$ -synuclein* gene on the long arm of chromosome 4 in the Contursi-kindred, an Italian family with dominantly inherited early-onset parkinsonism.<sup>10</sup> The same mutation (Ala53Thr) could later be found in several Greek families, and other mutations in the same locus, called *PARK1*, were identified in German, Spanish, and American pedigrees.<sup>23</sup>

In the following years several gene loci were found to be associated with autosomal-dominantly<sup>24-27</sup> or recessively<sup>28-30</sup> inherited parkinsonism (table 1). Most of the so far known gene mutations are associated with juvenile or early onset of the disease, and some of them become dominated by atypical features during the course of the disease.<sup>12</sup> The recently identified *leucine-rich repeat kinase 2* (*LRRK2*) mutations in the *PARK8* locus, however, appear to cause parkinsonism that resembles sporadic PD with respect to both clinical and demographical features.<sup>31</sup> While other known gene mutations in PD have been identified only in a small number of patients with familial parkinsonism, *LRRK2* mutations are shown to be more frequent, and prevalent in different populations and continents. In a sample of 435 Norwegian patients with well-documented PD and 28 of their relatives, 10 subjects (2.2%) had a specific (G2019S) *LRRK2* mutation. More recent studies indicate that the same mutation might account for in between 13% and 41% of PD cases in Ashkenazi Jews and



North African Arabs.<sup>32, 33</sup> Other *LRRK2* mutations were found in 8% of PD cases in a Basque population.<sup>27</sup> However, these prevalence rates are derived from selected patient cohorts. Whether and to which extent *LRRK2* or other gene mutations increase susceptibility for the disease in the general PD population has to be clarified in future studies.

Table 1. Loci and genes linked to Parkinson's disease

<b>Locus</b>	<b>Map position</b>	<b>Gene</b>	<b>Inheritance</b>	<b>Age at onset</b>	<b>Pathology</b>
<i>PARK1</i>	4q21	<i>α-synuclein</i>	Dominant	40s	LB
<i>PARK2</i>	6q25	<i>Parkin</i>	Recessive	20-40	No LB
<i>PARK3</i>	2p13	Unknown	Dominant	60s	LB, P+T
<i>PARK4</i>	4q21	<i>α-synuclein</i>	Dominant	30s	LB, V
<i>PARK5</i>	4p14	<i>UCH-L1</i>	Dominant	> 55	Undetermined
<i>PARK6</i>	1p35-37	<i>PINK1</i>	Recessive	20-40	Undetermined
<i>PARK7</i>	1p36	<i>DJ-1</i>	Recessive	20-40	Undetermined
<i>PARK8</i>	12p11.2-q13.1	<i>LRRK2</i>	Dominant	50-70	LB, pleomorphic
<i>PARK10</i>	1p32	Unknown	Unclear	50-60	Undetermined
<i>PARK11</i>	2q34	Unknown	Unclear	Late	Undetermined

LB: nigral degeneration with Lewy bodies; P+T: plaques and tangles in some  
V: vacuoles in hippocampal neurons

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However, genetic causes have not been identified in the majority of PD cases. Twin-studies in which confounding effects are minimized due to similar or identical familial environment and genetic factors, demonstrate relatively low concordance rates in monozygotic twins, indicating that environmental factors are important in the etiology of PD,<sup>34</sup> particularly in those with typical age at onset of the disease.<sup>35</sup> A caveat of this conclusion, however, is the lack of power in twin-studies to reliably detect incompletely penetrant genetic mutations.<sup>36</sup>

Various conditions have been suggested to increase the risk for developing the disease. A meta-analysis on environmental risk factors and PD reported combined odds ratios of 1.26 for chronic well-water use, 1.56 for living in rural areas, and 1.85 for pesticide exposure.<sup>37</sup> In the Honolulu Heart program, following 8000 men prospectively for thirty years, working on a plantation for more than ten years was associated with a relative risk (RR) for PD of 1.7.<sup>38</sup> Due to the recognized association between manganese toxicity and parkinsonism, welders were thought to be at increased risk for PD. However, recently published large cohort studies argue against a relationship between welding and PD.<sup>39</sup> In several studies investigating life-style risk factors for PD, coffee and alcohol drinking was inversely associated with the prevalence of the disease.<sup>40</sup> Most consistently, however, cigarette smoking was found to be less frequent among patients with PD than controls. A recent meta-analysis of prospective studies concluded that patients with PD are at about half the risk to ever have smoked compared to controls (RR 0.51).<sup>41</sup> Analysis of subgroups revealed that, compared to never-smokers, the risk for PD was lowest for current smokers (RR 0.35) and intermediate for past smokers (RR 0.66). In addition, a dose-response relationship has been observed in several studies, with those smoking most intensively having the lowest risk of PD. However, risk estimates are different in men and women. Several case-control studies found an inverse relationship between smoking and PD in men, but not in women. Similar observations were made regarding the association between coffee consumption and PD. Therefore, a modulating effect of estrogen has been hypothesized.<sup>42</sup>

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There are several potential biological mechanisms for the reverse relationship between smoking and PD. Direct activation of cholinergic nicotinic receptors in substantia nigra and striatum protects dopaminergic neurons against toxicity in culture.<sup>43</sup> Inhibition of monoamine oxidase enzymes by nicotine might enhance elimination or suppress the formation of toxins.<sup>44, 45</sup> Induction of cytochrome P-450 enzymes by polycyclic hydrocarbons contained in cigarette smoke has been suggested to contribute to detoxification of environmental toxins that might cause parkinsonism, such as MPTP.<sup>46</sup> Furthermore, nicotine metabolites may be cytoprotective and avoid or slow down neurodegenerative processes.<sup>47</sup>

However, despite the apparently convincing findings in in-vitro and animal studies, there is still a lack of direct evidence of any neuroprotective effect of smoking with respect to the development and progression of PD in humans. Therefore, some authors suggest that this association might be due to other reasons. For instance, the effect of smoking could be only a symptomatic one, without any neuroprotective properties. Selective mortality of smokers also has been introduced as a potential confounder of the inverse relationship between smoking and PD, but prospective studies argue against this hypothesis.<sup>48</sup> Alternatively, the lack to develop strong smoking habits might be an early symptom of the disease, reflecting a distinct premorbid personality of patients with PD, characterized by wariness, introversion, compulsiveness, inflexibility, industriousness, and seriousness.<sup>49</sup> Compared to controls, PD patients score lower on a personal trait called novelty seeking and higher on a trait called harm avoidance, which both may be associated with dopaminergic function in the caudate.<sup>50, 51</sup> Extreme and unusual behaviors including alcoholism are significantly more common in control subjects than patients with PD.<sup>52</sup> Finally, gene-environment interactions have been suggested to modify the association between smoking and risk for developing PD.<sup>53-55</sup>

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## 1.4 Molecular pathogenesis of PD

The discovery of mutations in several genes and the increased understanding of dysfunction of their aberrantly encoded proteins have provided important and novel insights into the molecular pathogenesis of the disease. There is now increasing evidence that oxidative stress, mitochondrial dysfunction, and impairment of the ubiquitin-proteasome system (UPS) may represent the central molecular pathways and events in the pathogenesis of PD.

However, also prior to the identification of gene mutations in PD both mitochondrial dysfunction and oxidative stress were considered to play a role in the pathogenesis of the disease. Defects in mitochondrial complex-I of the respiratory chain were consistently found in the SN of patients with PD.<sup>56</sup> Further evidence of an involvement of complex-I in the pathogenesis of PD was provided by the observation that MPTP, an inhibitor of complex-I and contaminant of the manufacture of synthetic opiates, caused a syndrome resembling PD in drug abusers.<sup>57</sup> MPTP is characterized by selectivity for dopaminergic neurons and induces intracellular inclusions that contain  $\alpha$ -synuclein, resembling Lewy bodies. MPTP, which is similar to the widely used herbicide paraquat, leads to selective loss of nigrostriatal dopaminergic neurons.<sup>58</sup> Also rotenone, a common fish poison, induces parkinsonism in animals, but in contrast to MPTP and paraquat, via non-selective inhibition of complex-I.<sup>59</sup> The observation that it still leads to selective degeneration of dopaminergic neurons implies a vulnerability of dopaminergic neurons to complex-I deficits.

The physiological function of  $\alpha$ -synuclein is widely unclear, although findings from mice models suggest that it may be important for synaptic vesicle recycling with relevance for dopamine storage and dopamine transmission.<sup>60</sup> As fibrillar forms of  $\alpha$ -synuclein are one of the major components found in Lewy bodies, and increased levels in fibrillar  $\alpha$ -synuclein are thought to be toxic to neurons, it may play a key role in the pathogenesis of PD. Mechanisms by which  $\alpha$ -synuclein aggregates in PD are, however, not fully understood. As mentioned above, mitochondrial complex-I

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inhibitors and oxidative stress lead to aggregation of  $\alpha$ -synuclein. Also proteosomal inhibition in-vivo is associated with increased levels of fibrillization of  $\alpha$ -synuclein, as well as clinical symptoms of PD.<sup>61</sup> On the other hand, overexpression of  $\alpha$ -synuclein promotes mitochondrial deficits and increases sensitivity to oxidative stress and dopamine-mediated toxicity.<sup>62, 63</sup> In addition, recent studies suggest that interactions (“cross-seeding”) between  $\alpha$ -synuclein and amyloidogenic proteins like tau and  $\beta$ -amyloid may promote the fibrillization of both proteins and play a role in the pathogenesis of PD.<sup>64</sup> Thus, the pathophysiology underlying  $\alpha$ -synuclein aggregation and toxicity is complex, and the precise mechanisms and particularly their temporal order are still unclear. Therefore, we currently do not know whether  $\alpha$ -synuclein aggregation is the underlying cause or the consequence of mitochondrial dysfunction.

Parkin is involved in the UPS as an ubiquitin-ligase, and strong evidence suggests that loss of function of *parkin* is responsible for young-onset PD in affected patients.<sup>65</sup> Interestingly, inactivation of *parkin* did not lead to accumulation of putative parkin substrates in the UPS, dopaminergic cell loss, or parkinsonian symptoms in knockout mice models, although mild alterations of dopaminergic transmission were found.<sup>66</sup> In contrast, loss of neurons in the noradrenergic locus coeruleus were observed, as well as decreased mitochondrial respiratory capacity and age-dependent increase in oxidative damage in substantia nigra.<sup>67</sup> These findings strongly suggest an involvement of parkin in the regulation of normal mitochondrial function. Also mutations in *PINK1* and *DJ-1*, which likewise *parkin* cause recessively inherited forms of parkinsonism, have been linked to mitochondrial dysfunction and oxidative stress.<sup>12</sup> The mechanisms by which *UCH-L1* and *LRRK2* gene mutations are involved in the etiology of PD are currently poorly understood and remain to be clarified.

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## 1.5 Neurochemistry and neuropathology of PD

The pathology of PD is complex, and its pathophysiology and pathogenesis are in parts not well understood. Although dopamine depletion and cell loss in the nigrostriatal tract, together with the presence of Lewy bodies, are the neurochemical and neuropathological hallmarks of PD, there is increasing evidence for dysfunction also in other areas of the brain and involvement of pathways other than the dopaminergic. While the classical motor features mainly relate to dopaminergic pathology, other motor symptoms and particularly non-motor problems are likely to reflect changes in non-dopaminergic transmitter systems.<sup>9</sup>

PD does not become clinically evident before a substantial loss of dopaminergic neurons is reached, probably due to compensatory mechanisms both pre- and postsynaptically in the nigrostriatal system.<sup>68</sup> Based on neuropathological data, a 60% to 80% loss of striatal dopaminergic terminals is needed to induce parkinsonian symptoms,<sup>69, 70</sup> and the rate of nigral degeneration in patients with PD is eight to ten times higher than in healthy age-matched controls. Neuroimaging studies indicate a progressive degeneration in the striatum of 4% to 13% per year in PD.<sup>71, 72</sup> Whether the presymptomatic period is long-lasting or begins in rather close temporal relation to the clinical onset is uncertain and object of ongoing research.<sup>20, 72</sup>

Reduced activity in non-dopaminergic transmitter systems such as the cholinergic, noradrenergic, serotonergic, and glutamatergic, has also been found in patients with PD.<sup>73</sup> Studies indicate that these changes may be present even at the clinical onset of the disease and become more prominent in advanced stages. In line with these neurochemical findings, also pathological studies provide evidence of degeneration outside the classical pathway of substantia nigra. Lewy bodies and cell loss have been found in different areas of the brain, including brainstem nuclei, prefrontal region, and cortex.<sup>74</sup> More recent findings from two clinicopathological studies indicate that pathological changes typical for PD, Lewy bodies and  $\alpha$ -synuclein pathology, may evolve sequentially, starting in brainstem and spreading to midbrain, mesocortex, and

eventually neocortex.<sup>75, 76</sup> Based on their findings, Braak and colleagues suggest a staging of PD pathology from stage 1 to stage 6, in which clinical symptoms become evident at stage 3 (table 2). In this stage, typical pathological changes, Lewy neurites and Lewy bodies, have already spread from lower brainstem regions including the olfactory tract and vagus nerve to substantia nigra. This would explain why olfactory deficits precede the emergence of motor symptoms in a considerable portion of patients with PD.<sup>77</sup> Although there is no doubt that depleted dopamine and cell loss in substantia nigra play a central role in the pathogenesis of PD, these findings also question whether the nigrostriatal pathway is primarily affected in PD, or secondary to changes in other areas of the brain.

Table 2. Staging of brain pathology in idiopathic PD according to Braak et al.<sup>75, 76</sup>

Stage		Pathology	
1	Medulla oblongata	Dorsal IX/X motor nucleus and/or intermediate reticular zone	Presymptomatic
2	Medulla oblongata and pontine tegmentum	Stage 1 plus caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus-subcoeruleus complex	↓
3	Midbrain	Stage 2 plus midbrain including substantia nigra pars compacta	Symptomatic
4	Basal prosencephalon and mesocortex	Stage 3 plus prosencephalon, temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus)	↓
5	Neocortex	Stage 4 plus high order sensory association areas of the neocortex and prefrontal neocortex	↓
6	Neocortex	Stage 5 plus first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field	↓

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## 1.6 Cardinal features and presenting symptoms of PD

Parkinsonism is a clinical diagnosis and defined by the presence of at least two of the four motor signs tremor, rigidity, bradykinesia, and postural abnormalities.<sup>78</sup>

Parkinsonian tremor is typically present at rest with a frequency of 4 to 6 Hz. It is usually asymmetric at disease onset, often affects the upper extremity, but may also be seen in the foot, particularly later during disease progression. Involvement of the head is atypical at the beginning of the disease and more typical for essential or dystonic tremor. Resting tremor is usually lost during sleep, reduced in action, and worsened by excitement, anxiety, or apprehension.

Rigidity is a form of resistance to passive stretch of skeletal muscles. It is independent of the speed of motion and may become apparent as a cogwheel-like resistance.

Bradykinesia describes slowness of movements with difficulties in initiating and maintaining motions. Patients with PD may also be unable to perform two motor tasks simultaneously or carry out sequences of motor tasks. Bradykinesia is considered to be one of the most disabling motor symptoms in PD and may become clinically apparent as micrographia, hypophonia, impaired finger dexterity, and difficulty in rolling over in bed, among others.

Postural abnormalities in PD are due to rigidity and loss of the righting reflex, resulting in characteristic changes in posture and problems with gait and balance. Rigidity affects slightly more flexor muscles than extensors, leading to stooped posture with flexion in trunk and neck, and reduced concomitant arm swing. The typical parkinsonian gait is small stepped, slow, and shuffling. The righting reflex, important to restore and maintain the posture when an external force is given suddenly to cause a perturbation of the balance, is impaired, resulting in propulsion, instability, and frequent falls.



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Besides the typical motor signs, other symptoms may be present when the disease becomes clinically manifest. Oily skin and seborrheic face are signs of autonomic dysfunction and due to increase in apocrine secretion rich in lipids. Also constipation is common in patients diagnosed with PD. The blood pressure tends to be lower, but symptomatic orthostatic hypotension is uncommon at disease onset. Frequent urination is often seen at onset of PD, but autonomic and atonic bladders are very uncommon. A considerable portion of patients reports olfactory dysfunction when clinical symptoms become apparent or even before. Although overt dementia is not typical in early stages of the disease, subtle cognitive dysfunction might be seen and detected by neuropsychological testing. Depressive symptoms may precede the onset of clinical symptoms in PD by several years or even decades. A more detailed description of the prevalence of motor and non-motor symptoms and their progression over time is given in section 1.9 “Disease progression in PD”.

## 1.7 Diagnosis and differential diagnosis of PD

Parkinsonism may be induced by agents that reduce dopamine-levels in the human brain, occur post-infectious, be due to vascular disease, or appear as part of other neurodegenerative diseases. However, most commonly parkinsonism is caused by PD in which, by definition, the clinical diagnosis has to be confirmed by neuropathological findings of Lewy bodies and cell loss in the nigrostriatal tract.

Parkinsonian symptoms may be subtle at the onset of the disease and misdiagnosis is therefore not uncommon.<sup>79</sup> Use of strict diagnostic criteria has been shown to increase the accuracy of clinical diagnosis in parkinsonian syndromes.<sup>80</sup> Features that clinically may help to distinguish PD from other parkinsonian disorders are asymmetry of motor symptoms, tremor at rest, and good response to levodopa treatment. Severe autonomic dysfunction, gaze palsy, and gait dysfunction at disease onset are uncommon and may indicate atypical parkinsonian disorders like multiple system atrophy (MSA) or progressive supranuclear palsy (PSP). A diagnosis of dementia with Lewy bodies (DLB) should be considered in patients with

parkinsonian features and early development of cognitive impairment, particularly in those with fluctuating hallucinations and other clinical signs of visuospatial or executive dysfunction. Parkinsonian features are also seen in a considerable portion of patients with Alzheimer's disease (AD). For a more detailed overview see table 3.

Table 3. Differential diagnosis in parkinsonian disorders

Type of parkinsonism	Subtype/cause
Parkinson's disease <sup>a</sup>	<ul style="list-style-type: none"> <li>• Idiopathic</li> <li>• Familial</li> </ul>
Symptomatic parkinsonism	<ul style="list-style-type: none"> <li>• Drug-induced               <ul style="list-style-type: none"> <li>• Neuroleptics, antidepressants, lithium</li> <li>• Antiemetics</li> <li>• Antihypertensive agents, antiarrhythmics</li> </ul> </li> <li>• Vascular disease</li> <li>• Intoxication (MPTP, rotenone, others)</li> <li>• Traumatic</li> <li>• Post-infectious</li> <li>• Neoplasm</li> <li>• Normal pressure hydrocephalus</li> </ul>
Parkinsonism due to other neurodegenerative disorders	<ul style="list-style-type: none"> <li>• Atypical parkinsonism               <ul style="list-style-type: none"> <li>• Multiple system atrophy (MSA)<sup>a</sup></li> <li>• Progressive supranuclear palsy (PSP)<sup>b</sup></li> <li>• Corticobasal degeneration (CBD)<sup>b</sup></li> </ul> </li> <li>• Dementia with Lewy bodies (DLB)<sup>a</sup></li> <li>• Alzheimer's disease<sup>b</sup></li> <li>• Others</li> </ul>

<sup>a</sup> Synucleinopathy; <sup>b</sup> Tauopathy

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## 1.8 Assessment of disease severity and progression in PD

### 1.8.1 Clinical assessment of parkinsonism and disability

There are several established clinical instruments to measure the severity and progression of motor symptoms and disability in PD:

The most widely used rating tool in PD is the Unified Parkinson's Disease Rating Scale (UPDRS), which was introduced in 1987 by an international group of movement disorders specialists.<sup>81</sup> The UPDRS was designed to follow the longitudinal course of the disease and has been shown to be both reliable and valid. It is divided in four parts (subscales), covering symptoms of mentation, behavior, and mood in part I, activities of daily living in part II, motor symptoms in part III, and complications of therapy in part IV. Each item in part I to III is quantitatively scored on a 5-point scale (from 0 to 4). Despite its strengths, the UPDRS is currently under revision to adapt it to recent scientific advances, particularly to better capture the wide spectre of non-motor problems experienced by patients with PD.

The Hoehn and Yahr scale<sup>82</sup> was devised in 1967 and is the other main scale used in PD. It measures the severity of the disease, including both impairment and disability of movements, balance, and gait, by allocating stages from 0 (no visible symptoms of Parkinson's disease) to V (parkinsonian symptoms on both sides and not able to walk). It has been shown to correlate with neuroimaging studies of dopaminergic loss and other clinical scales of motor impairment and disability. Non-motor symptoms are, however, not captured by the scale.

The Schwab and England scale<sup>83</sup> assesses the patients' ability to perform daily activities in terms of speed and independence on a range from 0% (bedridden, vegetative dysfunction, complete invalid) to 100% (completely independent, essentially normal).

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## 1.8.2 Clinical assessment of non-motor problems

### *1.8.2.1 Assessment of cognitive impairment and dementia*

There are several instruments to assess cognitive impairment and dementia in PD. In early stages of the disease, cognitive dysfunction may be subtle and thus not assessable by clinical rating tools. Hence, neuropsychological testing is helpful to detect early changes in cognitive function in patients with PD. However, it may also be useful in more advanced stages of the disease.

The Mini-Mental State Examination (MMSE)<sup>84</sup> is the most widely used and validated screening tool of cognitive impairment. It consists of 30 items covering orientation in time and space, recent and distant memory, attention, language, and the ability to follow simple verbal and written commands. The MMSE provides a total score indicating the cognitive function of an individual.

The Gottfries, Bråne & Steen Dementia Scale (GBS)<sup>85</sup> rates severity of dementia and provides a profile of the symptoms of dementia by estimating motor, intellectual, emotional, and other features characteristic of dementia in four subscales. Each item is scored on a clearly defined 7-point scale (0 indicates normal functioning and 6 indicates maximal severity). The rating is based on observation of the patient and an interview of the patient and a caregiver.

The Dementia Rating Scale (DRS)<sup>86</sup> is a commonly used cognitive rating instrument designed to assess the course of decline in dementia. It has five subscales measuring attention, initiation, construction, conceptualization, and memory. Scores range from 0 (maximal severity) to 144 (normal cognitive function). The DRS is a valid and reliable assessment tool of cognitive functioning in older adults.

The Diagnostic and Statistical Manual of Mental Disorders (DSM)<sup>87</sup> includes standardized diagnostic criteria for the diagnosis for several psychiatric disorders. The revised third and the fourth edition of the DSM define dementia as follows:

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“The essential feature of dementia is impairment in short- and long-term memory, associated with impairment in abstract thinking, impaired judgement, other disturbances of higher cortical function, or personality change. The disturbance is severe enough to interfere significantly with work or usual social activities or relationships to others. ...”

### *1.8.2.2 Assessment of fatigue*

Since fatigue is a subjective problem lacking objective correlates, it is most appropriately assessed by measuring the patient’s own perception of this complaint by self-report. A range of self-completed questionnaires has been developed to measure the severity of fatigue for clinical and research purposes. As fatigue in PD may overlap with other features such as depression and apathy, these should be assessed in parallel. In addition, other medical conditions may be considered as potential causes of fatigue.

The most widely used measurement instrument is the Fatigue Severity Scale (FSS),<sup>88</sup> a nine-item scale assessing the influence of fatigue on activities on daily living. Each item is graduated from 1 (strong disagreement) to 7 (strong agreement), and the mean score of the nine items is the patient’s score in FSS. Originally developed to measure fatigue in patients with multiple sclerosis, the FSS has been shown to be reliable and internally consistent. It is brief and easy to administer.

The Fatigue Assessment Inventory (FAI)<sup>89</sup> is an expanded version of the FSS, including 29 items. It assesses both quantitative and qualitative aspects of fatigue. Although the FAI demonstrates good psychometric qualities, its reliability has been characterized as only moderate, with only two of its four factors showing validity with other measurements of fatigue.<sup>90</sup>

The Fatigue Severity Inventory (FSI)<sup>91</sup> was developed for use in patients with PD, adapted from the FAI and extended to 33 items. The FSI has shown concurrent validity with other measurement instruments of fatigue.

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The Multidimensional Fatigue Inventory (MFI)<sup>92</sup> is a 20-item self-completed instrument measuring five dimension of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each dimension exists of four items which are rated from 1 (no fatigue) to 5 (very fatigued). It is a validated and reliable measurement instrument of fatigue.

Recently, a further measurement instrument of fatigue, designed for patients with PD, has been introduced. The Parkinson Fatigue Scale (PFS-16)<sup>90</sup> is a 16-item self-report instrument designed to assess physical aspects of fatigue and their impact on daily functioning. The PFS-16 shows high internal consistency and satisfactory test-retest reliability.

### **1.8.3 Neuroimaging in PD**

Structural brain imaging using computed tomography of the head (cranial CT) and magnetic resonance imaging (MRI) are expected to be normal in uncomplicated PD. It is, however, useful to exclude other conditions leading to parkinsonian symptoms, such as vascular parkinsonism, and may help to distinguish PD from other neurodegenerative syndromes like MSA and PSP.

Functional brain imaging is increasingly used in diagnostics of PD and for assessment of the severity and progression of the disease. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) using dopamine-ligands are the currently primary neuroimaging techniques in PD.<sup>93</sup> Reduced striatal dopamine-uptake or metabolism in the striatum, usually asymmetrical and more pronounced in the putamen than in the caudate, are typical findings in early PD. PET and SPECT are characterized by high sensitivity and specificity in distinguishing patients with PD from age-matched healthy controls. Studies of  $\beta$ -CIT SPECT with blinded readings reported diagnostic sensitivity of greater than 95% and specificity in between 83% and 100% for clinically probable PD compared with essential tremor.<sup>93</sup> However, none of these neuroimaging techniques reliably distinguishes PD from atypical forms of parkinsonism.

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Both SPECT and PET have increasingly been used in clinical trials to indirectly measure disease progression. A number of studies using imaging ligands have demonstrated that the reduction in ligand binding correlates with motor severity in PD.<sup>94-96</sup> This is particularly true for akinesia, axial symptoms, and, to a less extent, rigidity.<sup>97</sup> Interestingly, several studies found that tremor at rest and action tremor are not related to the degree of dopaminergic denervation measured by striatal dopamine transporter binding or dopamine metabolism.<sup>97</sup> However, recent results from studies using imaging endpoints to assess disease progression, as the ELLDOPA trial, question the validity of currently applied neuroimaging methods in assessing changes in disease severity in PD.<sup>98</sup> Low reproducibility due to scan-to-scan variability and confounding effects by study medication, leading to downregulation of dopamine transporter activity, are currently considered to be the main problems of neuroimaging techniques used in PD.<sup>99</sup> In addition, measuring dopamine metabolism or dopamine transporter activity only appears to be insufficient in reflecting the severity or progression of a disease in which a variety of symptoms are due to non-dopaminergic involvement. More recently, functional imaging using acetylcholine esterase (AChE) and choline acetyl transferase (ChAT) radioligands has been introduced to assess neurochemical deficits in cholinergic pathways in PD,<sup>100</sup> and carbon-11 labeled RTI-32 PET was used to study the role of catecholaminergic neurotransmission in depression of patients with PD.<sup>101</sup> However, these and several other tracers are thus far reserved to research purposes.

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## 1.9 Disease progression in PD

### 1.9.1 Motor symptoms and disability

**Tremor** at rest is the most common motor symptom at disease onset, prevalent in 60% to 70% of patients with PD.<sup>102-104</sup> However, 25% of patients with PD never develop tremor.<sup>103</sup> **Bradykinesia and rigidity** are less common, but still frequently seen at onset of PD. The usually good clinical response of these cardinal features to levodopa treatment and their correlation with changes in dopamine transporter activity and dopamine metabolism in neuroimaging studies implies underlying deficits in the dopaminergic nigrostriatal system. In the very majority of patients, the initial motor symptoms are localized to the upper extremities,<sup>105</sup> spreading to the other ipsilateral limb within one to three years and affecting the contralateral limbs in three to eight years.<sup>106</sup> The asymmetrical pattern, however, usually persists during the course of the disease, even in advanced stages.<sup>80</sup>

**Axial symptoms**, including postural instability and impairment of speech, are not typical at disease onset, but become a common complication of advanced PD. In a community-based study of 128 patients with PD, 64% had postural instability with falls and 49% had speech difficulties at an average of six years of disease duration. Only 1% of these patients reported unsteadiness as their initial symptom.<sup>107</sup> The control of balance and gait is complex, involving brainstem and midbrain locomotor areas, and motor cortex.<sup>108</sup> However, findings from several studies provide evidence that degeneration in cholinergic brainstem nuclei, particularly the pedunculopontine nucleus (PPN),<sup>108, 109</sup> is crucial for development of postural instability and gait problems which both increase the risk of falls and injuries. About 70% of patients with PD fall at least once each year.<sup>110</sup>

**Freezing of gait** (FOG) is an important source of falls.<sup>111</sup> FOG describes the patients' difficulty to move their feet and may become apparent as start-hesitation or halting when walking. FOG often occurs suddenly, may be triggered by visual stimuli like



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narrow spaces and doors, tends to be transient, and may appear both in on- and off-state. In the DATATOP trial, 7% of patients with mild PD reported FOG before treatment was initiated.<sup>112</sup> 26% of patients experienced FOG at the end of the study. In a long-term study, 42 of 52 patients (81%) had fallen due to the disease.<sup>113</sup> FOG is strongly associated with the severity of the disease, while the duration of the disease per se does not seem to be a major risk factor. The pathophysiological basis of this phenomenon is poorly understood, but a strong association with development of axial symptoms may indicate common underlying pathology.<sup>112</sup>

Although the nature of PD is usually described as slowly progressive, only few prospective studies have given estimates on **the rate of functional decline** in PD using currently acknowledged clinical rating scales. Drug trials including placebo arms provide information on the natural progression of motor symptoms in patients with early disease, estimating the rate of progression in drug-naïve PD patients to be 3.6 to 13.4 points per year, as measured by the UPDRS motor score.<sup>114, 115</sup> Using the same assessment tool, progression rates in treated patients ranged from 0.7% to 1.5% in two longitudinal cohort studies, one of which was population-based.<sup>116, 117</sup> Interestingly, subscores for bradykinesia, rigidity, and gait and balance were found to progress similarly, while tremor subscores did not worsen over time, possibly indicating different underlying pathophysiological processes.<sup>116</sup>

Information on the natural long-term disease progression in PD comes from studies conducted in the pre-levodopa era, but is limited. In a study by Mjølne, 40% of patients developed impairment of work ability within the first four years of disease duration.<sup>118</sup> Hoehn and Yahr, in their classic article, reported that 37% of patients with PD had reached stage stage III or above within four years of disease duration, while 34% of those with a disease duration for ten years or more still were in stage I or II.<sup>82</sup> Surprisingly, more recent studies suggest that the rate of functional decline is similar in treated patients. Müller et al. studied the progression of Hoehn and Yahr stages in patients with pathologically confirmed PD and found no patient with progression to Hoehn and Yahr stage III within the first year of motor onset.<sup>119</sup> In the

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same study, median duration from debut to Hoehn and Yahr stage II and III was 3 years and 5.5 years, respectively, similar to the results published by Hoehn and Yahr. In a prospective long-term study following treated PD patients for 15 years, the mean UPDRS ADL score was 18 in on- and 24 in off-state, and the average Hoehn and Yahr stage was 3.8 and 4.1, respectively.<sup>113</sup> The authors also compared data on the Hoehn and Yahr staging in their patients with those from the pre-levodopa study by Hoehn and Yahr and found no differences in long-term results. They concluded that modern treatment does not lead to significant long-term benefit in patients with PD.

There is a remarkable interindividual variation in the progression of PD, which has resulted in numerous studies investigating predictors of more or less rapid decline in the disease. Hoehn and Yahr, similar to others, suggested that the progression of the disease might be slightly less rapid when tremor is the initial symptoms, at least during the first ten years of disease duration.<sup>82</sup> They found no association between age at onset of the disease, gender, or family history, and the rate of disease progression in their cohort. In contrast, higher age at disease onset was a major determinant of the course of the disease in the Sydney multicentre study, while other features including balance problems and symmetrical disease onset were not.<sup>120</sup> In a case control study, age at onset but not exposure to chemicals and herbicides, well-water drinking, rural living, or smoking was associated with more rapid progression to Hoehn and Yahr stage III.<sup>121</sup> In a population-based study, a diagnosis of dementia, higher disability and longer disease duration predicted more impaired motor function, while age at onset did not.<sup>116</sup> Marras et al. reviewed these and other studies to summarize evidence on predictors of disease progression in PD.<sup>122</sup> Of more than 450 articles obtained for review, only 13 met the authors' criteria for inclusion, including prospective and longitudinal design. However, of the included studies, many had methodological weaknesses, leading to inconsistent or conflicting evidence on several potential risk factors of functional decline, including age, age at onset, disease duration, and disease subtype. Thus, uncertainty remains about the prognostic importance of most factors.

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### 1.9.2 Motor complications

During the course of the disease, a considerable portion of patients with PD develops motor complications. These comprise dyskinesias, which are episodes of abnormal involuntary movements involving head, trunk, and limbs, and motor fluctuations, describing a transient decline in motor performance. Both dyskinesias and motor fluctuations increase in frequency with increase in disease duration.

In clinic-based studies, approximately 40% of patients developed motor problems within four to six years after disease onset.<sup>123</sup> Hely et al. reported dyskinesias in 94% and “end of dose failure” in 96% of patients with mean disease duration of about 17 years.<sup>113</sup> However, these may be overestimates of motor complications due to selection bias. Population-based studies are consistent in their finding of substantially lower prevalence rates of motor complications in PD.<sup>107, 124</sup> In a community-based study, 78% of the patients did not experience motor fluctuations after over 6 years of levodopa treatment.<sup>124</sup> In another population-based study from England, 28% of levodopa-treated patients suffered from dyskinesias and 40% from response fluctuations after about seven years of disease duration.<sup>107</sup>

The risk of developing motor complications has been linked to age of onset, disease duration and severity, and levodopa dosage. Patients with younger age at disease onset have consistently been found to better respond to levodopa treatment than those with late-onset PD, but at the expense of increased dyskinesias and motor fluctuations.<sup>125</sup> Several clinical trials have shown that those using levodopa only are at higher risk to develop motor complications compared to patients treated with dopamine agonists alone or in combination with levodopa. There is now compelling evidence that non-physiological, pulsative stimulation of dopamine receptors by levodopa induces motor fluctuations and dyskinesias, possibly due to changes in gene expression which subsequently lead to changes in signaling proteins, neuropeptides, and neurotransmitters, resulting in alterations in firing pattern and dopamine responsitivity.<sup>126</sup>

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### 1.9.3 Non-motor symptoms

Most patients with PD will suffer from non-motor problems during the course of the disease. In a cross-sectional study of 199 patients with PD, only 12% had no non-motor problems after seven years of disease duration.<sup>127</sup> While the majority of these symptoms become more frequent in later stages of the disease, others may occur independently from disease duration and even precede the clinical onset of motor symptoms. Sleep disturbances, autonomic dysfunction, olfactory deficits, pain, and in particular a wide range of neuropsychiatric problems including cognitive impairment may lead to substantially reduced functioning and quality of life.<sup>8</sup>

#### 1.9.3.1 Cognitive impairment and dementia

While severe dementia is not typical at disease onset, cognitive impairment may be present even in early stages of PD. Impairment in a range of neuropsychological tests was found in a series of 91 PD patients with mean disease duration of less than two years,<sup>128</sup> and in a community-based study more than half of non-demented patients had some form of cognitive impairment.<sup>129</sup> In another community-based survey in early PD, 36% of the patients had evidence of cognitive impairment.<sup>130</sup> The cognitive profile in patients with the disease varies somewhat, but executive impairment, including working memory and attention shift, and eventually visuospatial dysfunction characterize early cognitive impairment in PD.<sup>131</sup> In a study of 42 PD patients with mild cognitive impairment, 20% had dominant memory deficits, 30% exhibited predominantly executive impairment, and 50% had a more global cognitive impairment.<sup>129</sup>

The cognitive impairment in patients with PD is progressive. In a recently published population-based study, the mean annual decline on the MMSE in 129 patients with PD was found to be one point. However, while the change in score for nondemented patients was small, patients with dementia declined with 2.4 points per year.<sup>132</sup> With advance in PD, there is an increase in the severity and range of cognitive deficits, probably reflecting the involvement of cortical structures. Based on results from large

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community-based studies using standardized cognitive assessment and DSM-III-R criteria, prevalence rates of dementia range from 23% to 41%.<sup>133</sup> However, as dementia is associated with increased mortality,<sup>134</sup> cross-sectional studies are likely to underestimate the true frequency of dementia in PD (PDD). Following de novo patients with PD in 5 years, an Australian study estimated a cumulative prevalence rate of 36%. In a population-based survey of 224 PD patients with mean disease duration of 9 years at baseline, the cumulative prevalence of dementia after 8 years of follow-up was as high as 78%.<sup>135</sup> The risk for developing dementia is up to 6-fold higher in PD than in non-PD subjects,<sup>136</sup> and about 10% of patients with PD develop dementia per year.<sup>136, 137</sup> Overall, about 3-4% of patients with dementia have PDD.<sup>138</sup>

Prospective studies indicate that advanced age rather than higher age at onset is a risk factor for PDD.<sup>135,139, 140</sup> Other factors that are independently associated with increased risk for incident dementia in PD are mild cognitive impairment and severity of parkinsonism, particularly axial symptoms like postural instability and speech problems.<sup>135, 139-141</sup>

### 1.9.3.2 *Fatigue*

Fatigue is a subjective experience that can be defined as an overwhelming sense of tiredness, lack of energy, or feeling of exhaustion. It is frequently seen in the general population, both in developing and developed countries,<sup>142</sup> but is significantly more prominent in several neurologic, psychiatric and systemic diseases.<sup>143, 144</sup> Although fatigue is associated and may overlap with depressive symptoms, it is distinguishable from depression in which lack of self-esteem and despair or feelings of hopelessness are prominent features.<sup>145</sup> It is also different from apathy which is dominated by lack of motivation with reduced goal-directed behavior, diminished goal-directed cognition, and decreased emotional engagement.<sup>146</sup>

Fatigue is one of the most common and most disabling non-motor problems in PD and has substantially negative impact on cognitive and physical function, and quality of life in patients with the disease.<sup>147, 148</sup> In a clinic-based study, 58% of patients with

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PD reported fatigue to be among their three most disabling symptoms, and almost one-third rated fatigue as their most disabling symptom. As in other diseases, fatigue in PD may occur as a physical or mental problem, and both dimensions of fatigue are more prominent in PD compared to age-matched control, but are not correlated with each other.<sup>91</sup> Underlying causes of fatigue in PD are poorly understood. Pathological cytokines in certain areas of the brain may be implicated in the etiology of fatigue in patients with PD.<sup>149</sup> With SPECT, correlations between fatigue and reduced perfusion of frontal lobes in patients with PD were found.<sup>150</sup> Findings from several studies conducted during the recent years indicate that dopaminergic deficiency may at least partially contribute to mental and physical fatigue in PD. In a double-blind, placebo-controlled crossover study, levodopa significantly improved physical fatigue in 25 patients with PD.<sup>151</sup> In another study, pergolide, an agonist of both D1 and D2 dopamine receptors, but not bromocriptine, which has high and selective affinity to D2 dopamine receptors, reduced fatigue in patients with PD. The authors concluded that a functional correlation between D1 receptors and fatigue may exist in PD.<sup>152</sup>

Rather few clinical studies have focused on fatigue in patients with PD, and thus knowledge on the clinical development of this important non-motor feature is limited. As other non-motor symptoms, also fatigue may precede the onset of the disease. In their original article, Hoehn and Yahr listed generalized fatigue as the presenting symptom in 2% of patients with PD.<sup>82</sup> In patients with more advanced disease, cross-sectional studies found prevalence rates between 40% and 56%, and the frequency of fatigue was found to be still higher (75%) during off-state (table 4).<sup>153</sup> The latter observation suggests that the perception of fatigue changes in parallel with motor fluctuations. This may further support an involvement of dopaminergic transmitter systems in the etiology of fatigue in PD. In contrast, while findings on the relationship between fatigue and disease severity were somewhat controversial, clinical studies found associations with other non-motor problems such as depression and cognitive impairment, which suggests underlying non-dopaminergic pathology.<sup>154</sup> However, in a study of 66 PD patients without depression and

dementia, still 50% suffered from fatigue.<sup>155</sup> This was twice as much as in the general population and in patients with severe coxarthrosis.

Prospective longitudinal studies of fatigue in PD are not conducted. The only retrospective longitudinal survey we are aware of, was questionnaire-based and followed a rather small cohort of 26 patients.<sup>156</sup> Despite the methodological limitations of this study, its main finding of persistence of fatigue in the majority of patients was interesting, suggesting that fatigue in the vast majority of patients might be a direct consequence of disease related pathological changes.

Table 4. Prevalence of fatigue in PD

Investigator (year)	Sample	Number	Disease duration (yrs)	Prevalence (%)
Hoehn and Yahr (1967)	Clinic-based	183	at onset	2%
Van Hilten et al. (1993)	Clinic-based	90	6.4	43%
Karlsen et al. (1999)	Community-based	233	9.0	44%
Shulman et al. (2001)	Clinic-based	99	6.9	40%
Witjas et al. (2002)	Clinic-based	50	12.7	56%-75%
Herlofsen et al. (2003)	Clinic-based	66	7.3	50%

### 1.9.3.3 Other neurobehavioral disturbances

Neuropsychiatric problems are common in PD. In a population-based study of 139 patients with PD, 61% suffered from at least one neuropsychiatric symptom after 12 years of disease duration.<sup>157</sup> Of importance, charting the frequency of cognitive impairment, dementia, and fatigue was not part of this investigation. The most common behaviors found were depression (38%) and hallucinations (27%).

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**Depressive symptoms** are significantly more common in PD than in age-matched controls and patients with other chronic diseases.<sup>158, 159</sup> In most population-based cross-sectional surveys, depression rates range from 20% to 50%. Meara and colleagues, however, reported depression in 64% of PD patients in their community-based cohort from North Wales.<sup>160</sup> This variation is likely to be the result of methodological differences used in the respective studies. In most patients, depressive symptoms are of mild to moderate severity, while major depression is less frequent. In a population-based study, only 7.7% met DSM-III criteria of major depression, while 45.5% had mild depressive symptoms.<sup>159</sup> In those with dementia, however, the portion of patients suffering from major depression is substantially higher.<sup>161</sup> Despite the high frequency of depressive symptoms, suicide is not more common in patients with PD compared to the general population.

Those with a history of depression and reduced functional activity are at risk for development of both major and minor depression.<sup>162, 163</sup> Other features such as cognitive impairment, female gender, and age are controversial risk factors for depression in PD. The relationship to disease severity is not as clear as in other neuropsychiatric problems, as a considerable portion of patients develop depressive symptoms shortly after or even before the motor manifestation of the disease.<sup>164</sup>

The reasons underlying depression in PD are unclear, but there is evidence for involvement of dopaminergic, noradrenergic, and serotonergic systems.<sup>165</sup> Neuroimaging studies have shown changes in metabolism in frontal lobes, particularly on the left side,<sup>166</sup> and reduced binding to cortical serotonin receptors, indicating postsynaptic dysfunction. More recently, depressive symptoms were shown to inversely correlate with reduced dopaminergic and noradrenergic binding in the locus coeruleus and several regions of the limbic system.<sup>101</sup>

**Hallucinations** in patients with PD rarely occurred before the introduction of dopaminergic treatment.<sup>167</sup> Dopaminergic agents are therefore understood as an important cause to psychotic symptoms and abnormal behavior in PD. However, in several prospective studies no association between hallucinations and dosages of



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dopaminergic agents or treatment duration could be found.<sup>168, 169</sup> In contrast, other factors such as age, disease severity, and most consistently cognitive impairment were identified as risk factors for hallucinations in patients with PD.<sup>167</sup> Due to the latter observation, a current theory is that hallucinations origin from a combination of dopaminergic stimulation and a more widespread cerebral involvement. Thus, an increase in frequency is expected as the disease progresses.

Reported prevalence rates of hallucinations vary, most likely due to differences in patient selection and study design, and range from 10% to 39%.<sup>167</sup> In a population-based study from England, 23% of 124 patients with PD suffered from hallucinations after 6 years of disease duration, compared to 26.6% of patients with a mean disease duration of 12 years in a Norwegian cohort.<sup>168</sup> Longitudinal studies of hallucinations in PD are rare. In a prospective survey of 89 PD patients with a mean disease duration of about 10 years at baseline, hallucinations were progressive and persistent, affecting 33% at study entry and 44% of patients four years later.<sup>170</sup> In the same study and others,<sup>171, 172</sup> visual hallucinations were found to be the most common form, while auditory, olfactory and tactile hallucinations were less frequent and usually present together with visual hallucinations. Although the insight is and remains retained in most patients with PD, hallucinations are one of the main features leading to hospitalization and nursing home placement.<sup>173</sup>

Symptoms of **apathy**, similar to the sense of fatigue, may overlap with those of depression, but there is evidence that these conditions are separable from each other.<sup>146, 174</sup> Apathy is common in several neurodegenerative diseases, particularly in progressive supranuclear palsy (PSP), in which up to 80% of patients are affected, while coexisting depression is rather rare. Across diagnostic groups, functional disturbances of the anterior cingulum, which is reciprocally connected to limbic, frontal, and basal ganglia structures, were found to be related to apathetic behavior.<sup>175</sup>

There is a lack of longitudinal studies of apathy in PD, and thus there is an uncertainty whether and how characteristics of apathy may change over time. Observed frequency rates of apathy vary substantially, ranging from 17% to 70%.

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This variation has been attributed to use of different rating scales of apathy, different cut-off values, and other methodological differences.<sup>175</sup> In the so far largest and only population-based study of apathy in PD, 16.5% were diagnosed with apathy after 12.6 years of disease duration.<sup>157</sup> Results from several cross-sectional studies suggest that apathy is strongly associated with cognitive impairment and dementia, and also executive dysfunction.<sup>146, 174, 176</sup> Thus, in those with advanced PD higher prevalence rates of apathy are expected compared to patients with early disease.

#### *1.9.3.4 Sleep disorders*

During the last decade, scientific research on sleep disturbances has resulted in achievement of thorough knowledge on regulation mechanisms of the sleep/wake mechanisms.<sup>177</sup> It is now clear that several brainstem nuclei and their communicating pathways in the ascending arousing system through the hypothalamus and thalamus to the cortex play key roles in sleep disorders. As Lewy bodies and cell loss are found in these areas in PD, it is anticipated that disturbances of sleep and alertness, including **insomnia, hypersomnia, and parasomnias**, are experienced by a large number of patients with PD and other diseases belonging to the group of  $\alpha$ -synucleinopathies, such as MSA.<sup>178</sup> In addition to pathological changes in brain areas crucial for regulation of sleep and awakesness, other conditions may contribute to sleep problems in patients with PD as well. Dopaminergic drugs, particularly dopamine agonists, have been linked to different sleep complaints including insomnia, **excessive daytime somnolence**, and **sudden sleep attacks**.<sup>179, 180</sup> It may be possible that the neurodegenerative process underlying PD makes the patients vulnerable to drug induced sleep fragmentation, as well as hypersomnia. Also coexisting motor (e.g. nocturnal bradykinesia) and non-motor problems (e.g. depression, hallucinations, nocturia), as well as other conditions like obstructive sleep apnea may worsen sleep quality in PD. In general, sleeping problems increase during the course of the disease, both with regard to their frequency and severity. In two previous studies, 74% and 93% of patients with PD reported some kind of sleep disturbances.<sup>181, 182</sup>

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**Insomnia** is the most common sleeping problem in PD. In a population-based study, 60% of the patients complained about nocturnal sleeping problems after 9 years of disease duration.<sup>183</sup> In most of them, sleep fragmentation and early awakening were the major problems, while falling in sleep was not. In the same population, these sleeping problems were found to be main contributors to reduced quality of life.<sup>184</sup>

Severe **hypersomnia**, often called excessive daytime sleepiness (EDS), is also common in PD.<sup>185</sup> Evidence suggests that daytime somnolence in PD is not a consequence of nocturnal sleeping problems.<sup>186</sup> EDS has been found in 15% of PD patients in a population-based cohort with mean disease duration of nine years. Results from a longitudinal study of the same population suggest that EDS in PD is a persistent complaint when once experienced.<sup>186</sup> EDS is strongly associated with disease severity, indicating that underlying cerebral changes themselves may be of major importance.<sup>186</sup> However, dopaminergic agents may contribute as well.<sup>187</sup>

**REM sleep behaviour disorder (RBD)** is a parasomnia characterized by prominent motor activity due to loss of the normal skeletal muscle atonia during REM sleep. Patients with idiopathic RBD have been shown to be at increased risk to develop PD and other  $\alpha$ -synucleinopathies, and thus RBD may be an early sign of an evolving synucleinopathy.<sup>188</sup> It is particularly common in patients with MSA and DLB.<sup>188</sup> In PD, up to one-third of patients are affected.<sup>189, 190</sup> The clinical main features of RBD are vocalizations and movements of limbs and body. They can vary in intensity and duration, and complex behaviors such as walking and even punching are described, potentially leading to injuries of patients themselves or their partners.

The syndromes of **restless legs (RLS)** and **period limb movements during sleep (PLMS)** are other parasomnias that may be associated with and more common in PD. In a case-controlled study from India, 7.9% of PD patients at five years of disease duration complained about RLS compared to only 0.8% of control subjects.<sup>191</sup> In comparison, others reported a 19.5% prevalence in PD at a mean disease duration of 9.1 years.<sup>192</sup> Because plasma ferritin concentrations were lower in RLS with PD than in idiopathic PD, low ferritin levels have been suggested to contribute to the

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development of RLS in PD. Disturbances in central dopaminergic systems, however, seem to play a major role in the etiology of RLS in patients with PD.<sup>193</sup>

#### *1.9.3.5 Autonomic disturbances*

Although autonomic dysfunction, particularly orthostatic hypotension, is generally accepted to be a clinical marker of atypical parkinsonian disorders such as MSA, increasing evidence suggest that it is a frequent characteristic also in patients with PD.

A recent study of de novo patients with PD found decreased cardiac radioiodinated metaiodobenzylguanidine (MIBG) uptake, indicating that latent sympathetic nervous dysfunction is already present in patients with early, untreated PD.<sup>194</sup> In the same study, MIBG uptake and blood pressure responses decreased with increased disease severity, suggesting that vasomotor cardiac dysfunction is associated with the severity of the disease. This is in line with clinical observations of an increase in autonomic disturbances as the disease progresses. Symptomatic hypotension is rare in early PD. In a prospective study of 51 de novo patients with PD, only one showed clinical symptoms of hypotension.<sup>195</sup> In contrast, in a prospective clinic-based survey of patients with 6 years of disease duration and more advanced disease, 15.4% complained about symptomatic orthostatic hypotension. Other frequently experienced autonomic symptoms in this cohort were hypersalivation (14%), sexual dysfunction (18%), urinary problems (22%), sweating disorder (24%) and constipation (59%).

Surprisingly, except for cardiovascular dysfunction, autonomic symptoms do not correlate with the duration and severity of the disease, nor age at onset in most studies.<sup>196</sup> In contrast, advanced age was associated with autonomic failure in some, leading to the suggestion that an disease related amplification of aging effects may contribute to autonomic disturbances in PD.<sup>196, 197</sup>

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#### 1.9.3.6 Olfactory dysfunction

Olfactory dysfunction in PD includes impairment of odor detection, differentiation, and identification, and is persistent and not influenced by drug treatment.<sup>198</sup> While most previous studies did not find any association between olfactory deficits and severity of parkinsonism, more recently published papers conclude that there is at least some relationship to disease severity in PD, particularly during the early stages of the disease.<sup>199, 200</sup> Prevalence rates of hyposmia in PD vary depending on which approach is used to identify the olfactory dysfunction. Most of the patients with PD showing deficits in olfactory tests are unaware of a smell disorder.<sup>201</sup> In a German study, 24% of 37 patients with PD reported to have had impaired olfactory function prior to the diagnosis of PD, 38% experienced subjective smell loss at the time or after diagnosis of PD, and the remaining 38% had subjectively normal olfaction after about 5 years of disease duration.<sup>200</sup> In contrast, based on olfactory testing, all suffered from impaired olfactory function with more than 50% of the patients diagnosed with anosmia.

In the light of Braak's hypothesis of a stagewise progression of pathological changes in PD, indicating presymptomatic lesions in the olfactoric tract, attention has been drawn to patients primarily diagnosed with idiopathic hyposmia. These are now shown to be at rather high risk to develop PD later during life.<sup>202</sup> Of 40 hyposmic, asymptomatic first-degree relatives of PD patients, 10% developed clinical PD within two years of follow-up. In addition, baseline 123β-CIT binding ratios of these patients were strongly reduced, indicating a subclinical degenerative process within the dopaminergic nigrostriatal system. Interestingly, in the remaining non-parkinsonian relatives with hyposmia the rate of decline in dopamine transporter uptake was significantly increased compared to relatives without olfactory dysfunction.

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## 1.10 Treatment of PD

There is no causal treatment available, and thus pharmacological therapy is still aimed at controlling motor signs and, to a less extent, non-motor symptoms in PD. Information about the disease and treatment strategies, as well as patient organisations, should be given as soon as possible during the course of the disease. Patients also should be informed about non-pharmacological treatment strategies of motor and non-motor symptoms, including physiotherapy and speech therapy.

### 1.10.1 Drug treatment of motor symptoms

**Levodopa** is a precursor of dopamine that is actively transported across the gut wall and passes the blood-brain barrier. It is taken up by dopaminergic neurons and decarboxylated to dopamine in the presynaptic terminal where it replaces dopamine lost by degeneration of substantia nigra. Levodopa is usually given in combination with a peripheral decarboxylase inhibitor (carbidopa or benserazide) to reduce peripheral side effects and to improve therapeutic effects. Although a wide range of differently acting agents has been developed since its introduction in the 1960s, levodopa is still considered to be the most effective drug therapy in PD.<sup>6</sup> The vast majority of patients with PD starting treatment with levodopa experience good to excellent functional benefit. However, with longterm use, levodopa therapy is associated with more frequent development of motor fluctuations and dyskinesias compared to other dopaminergic drugs, probably due to pulsative stimulation of dopamine receptors. As patients with older age at disease onset are less likely to develop motor complications and have a rather short life-expectancy, levodopa is the preferred treatment in these patients.

**Dopamine agonists** directly stimulate postsynaptic dopamine receptors without undergoing oxidative metabolism.<sup>203</sup> They have a longer duration of action than levodopa and do thus not expose dopamine receptors to rapidly fluctuating levels of stimulation. Such unphysiological stimulation is thought to underlie the development

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of motor complications. Several controlled trials have shown that initial therapy with dopamine agonists is associated with less rapid development of motor fluctuations and dyskinesias compared to initial treatment with levodopa.<sup>204</sup> The most recently developed dopamine agonists mainly stimulate D2- receptors, leading to less frequent side-effects than traditional dopamine agonists such as pergolide. Most common side effects are nausea, vomiting, and orthostatic hypotension. To avoid or reduce these, the dose of dopamine agonists is usually increased slowly, particularly in newly diagnosed patients. Dopamine agonists may also be given to patients with advanced disease who experience loss of efficacy during levodopa therapy. However, given in monotherapy, dopamine agonists are preferred in patients with younger age.<sup>205</sup>

**Catechol-O-methyltransferase (COMT) inhibitors** increase half-life and bioavailability of levodopa by inhibiting its conversion into 3-O-methyl-dopa. Entacapone is a peripheral COMT inhibitor and currently approved for adjunctive treatment in patients with motor fluctuations. Administered in combination with levodopa it reduces daily off-time and increases on-time. Because entacapone enhances the dopaminergic effect of levodopa, vomiting, dizziness, and particularly dyskinesias are typical side effects.

**MAO-B inhibitors** like selegiline inhibit the degradation of dopamine in the striatum. Several studies show less rapid disease progression in patients treated with selegiline,<sup>206, 207</sup> which may indicate neuroprotective properties, but results are not conclusive. Selegiline has only weak symptomatic effect and is generally well tolerated. However, due to metabolism to amphetamine, it may increase blood pressure, sleep problems, and euphoria. Used in adjunctive therapy it also may potentiate side effects of other antiparkinsonian drugs. Recently, another irreversible MAO-B inhibitor, rasagiline, has been introduced in the treatment of PD.<sup>208</sup> Rasagiline has shown similar clinical effects as entacapone with respect to improvement of motor function and motor fluctuations. It is approved for use as initial monotherapy and adjunctive treatment in moderate-to-advanced PD. Unlike selegiline, rasagiline is metabolized to aminoindan and thus free from

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amphetamine-related side effects. Also rasagiline may have disease-modifying properties, but further studies are needed before firm conclusions can be drawn.

**Amantadine** and **anticholinergic drugs** are no longer recommended for routine use in PD in Norway due to limited symptomatic effect and an unfavorable profile of adverse effects including worsening of behavioral and autonomic function.

### 1.10.2 Drug treatment of non-motor symptoms

In recent years, several placebo-controlled trials indicated that **cholinesterase inhibitors** (ChEI) improve cognition and psychiatric symptoms, as well as global function in patients with PDD.<sup>209</sup> In the so far largest randomized, placebo-controlled trial including 541 patients with PDD, treatment with rivastigmine resulted in a moderate improvement in global ratings of dementia, cognition, and behavioral symptoms after 24 weeks of follow-up.<sup>210</sup> However, the majority of patients who were treated with rivastigmine (80.2%) had no clinically meaningful improvement. Interestingly, the occurrence of hallucinations in rivastigmine-treated patients was half of that in untreated subjects, indicating that ChEI may have antipsychotic properties. The most frequent adverse events observed in treatment with ChEI were nausea, vomiting, and worsening of tremor.

Clinical experience and epidemiological studies suggest that hallucinations in PD are mainly visual and non-threatening, and associated with advanced disease. Although the underlying pathophysiology is poorly understood, treatment with dopaminergic agents is thought to play a major role. However, also other medical conditions like infections, fever, and electrolyte disturbances may exacerbate hallucinations and should be eliminated before dose reduction of dopaminergic agents is considered. Typical antipsychotic drugs may improve hallucinations, but also worsen parkinsonism due to their antidopaminergic properties. Therefore, treatment with atypical antipsychotics, which are characterized by rather low D2-receptor antagonism, is broadly recommended in PD patients with hallucinations. **Clozapine** has been shown to reduce hallucinations without worsening motor symptoms, but is



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associated with a range of side effects. Because it also may lead to life-threatening agranulocytosis, frequent monitoring is required. This strongly limits its use in everyday practice. Therefore, other atypical antipsychotic drugs, particularly **quetiapine**, are generally preferred in treating hallucinations in PD. However, it is worthwhile to note that atypical antipsychotics including **risperidone** and **olanzapine** failed to significantly improve hallucinations in PD in a number of controlled trials. In line with this, a recently published double-blind, placebo-controlled trial in PD patients with hallucinations revealed no benefit of quetiapine compared to placebo.<sup>211</sup>

Depressive symptoms and their pharmacological treatment with **serotonine reuptake inhibitors** (SSRI) are common in PD. Also **tricyclic antidepressants** (TCA) are used in the treatment of depression in PD. However, the number of well-designed clinical trials of antidepressants in patients with PD is limited. A recent meta-analysis concluded that both active treatment and placebo improved depressive symptoms to a similar extent.<sup>212</sup> In contrast, results from the same study indicated that patients with PD may benefit less from antidepressants than elderly depressed patients without the disease.

**Modafinil** is a wakefulness promoting agent approved for use in narcolepsy and has recently been investigated for efficacy and tolerability in PD patients with EDS. The results show good tolerability in patients with PD, but some inconsistency regarding efficacy, with improvement in subjective but not objective measurements of daytime somnolence.<sup>213, 214</sup> However, in the most recent and so far largest double-blind, placebo-controlled trial, modafinil failed to improve EDS measured by both the Epworth Sleepiness Scale (ESS) and the multiple sleep latency test (MSLT).<sup>215</sup>

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### 1.10.3 Surgical treatment

Surgical treatment in PD is still reserved to patients with both advanced disease and motor complications. Although **lesioning surgery**, particularly by pallidotomy, is considered efficacious in treatment of PD, **deep brain stimulation (DBS)** has become the gold standard in surgical treatment of PD during the last decade.<sup>216</sup> Main advantages of DBS compared to ablational surgery are its reversibility and the possibility of adjustment over time. DBS of the subthalamic nucleus (STN) has become the most widely used surgical treatment of motor complications in PD. Careful patient selection is important to achieve good clinical response after STN DBS. Younger age and good levodopa-responsiveness predict a favorable outcome. Recent studies indicate that DBS of the STN provides substantial long-term benefits regarding motor function and motor complications. Five years after STN implantation, motor function measured by UPDRS III was still improved 54% “off”-medication and even 73% “on” drug.<sup>217</sup> Severity of levodopa related motor problems was decreased by 67% and daily levodopa dosages reduced by 58%. However, STN DBS does not halt disease progression based on results from neuroimaging study measuring disease progression by 18F florodopa PET.<sup>218</sup> DBS of the globus pallidus interna (GPi) provides similar improvement of motor function and motor complications compared to STN stimulation, but has less impact on drug dosages.<sup>219</sup> Treatment with DBS of the thalamic ventralis intermedius nucleus (Vim) is less common in PD, but may be helpful in those with predominant resting tremor.

During the 1990s, several open studies reported improvement of motor function after **transplantation of embryonic dopaminergic grafts** into the putamen and caudate in PD. However, fetal nigral transplantation is currently far from being a treatment option in PD after two more recently published double-blind, sham-controlled trials reported no overall treatment benefit.<sup>220, 221</sup> In contrast, high frequencies of adverse events, particularly “off”-medication dyskinesias, were observed in up to 56% of transplanted patients within two years after surgery.

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## 1.11 Prognosis and socioeconomic consequences of PD

PD is chronic and progressive, and currently incurable. No treatment is proven to halt the progression of the disease. Life expectancy is decreased despite modern treatment. In their classic article, Hoehn and Yahr reported a standardized mortality ratio (SMR) of 2.9.<sup>82</sup> SMR derived from later studies range from 1.3 to 4.1.<sup>222, 223</sup> Methodological differences are likely to account for this variation. In a study identifying incident cases of PD in Olmstead County between 1976 and 1995, median survival of patients was 10.3 years.<sup>224</sup> In the Sydney Multicentre Study following de novo patients randomly assigned to levodopa or bromocriptine, the median time from onset of the disease to death was 12.2 years.<sup>113</sup> Interestingly, patients originally assigned to levodopa survived longer than those using bromocriptine. Disease severity, dementia and, with some inconsistency, age are independent risk factors for increased mortality.<sup>222, 223</sup> The cause of death in patients with PD are often related to immobility, and fatal infections are not unusual.<sup>225</sup>

Economic investigations of the costs of PD have not been done in Norway yet, but several studies from Western and Northern European countries show that the disease is costly for patients and the society.<sup>226-228</sup> In a Swedish survey, the total annual cost of the disease was estimated to be 13,800 Euros per individual.<sup>226</sup> Due to the progressive nature of PD, costs increase with disease severity. Direct annual costs were estimated to be nearly 30,000 Euros for those in Hoehn and Yahr stage V, and nursing home placement was associated with a cost increase of approximately 500% in English patients.<sup>228</sup> Due to the aging population, the economic burden of PD is expected to further increase in future.

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## 2 Aims of the study

The primary objectives of this thesis were to describe and achieve a better understanding of aspects related to the clinical disease progression in Parkinson's disease (PD). To obtain this information we have

- in study 1 examined the frequency of cigarette smokers in a population-based cohort of patients with PD and two control groups, and investigated the progression of parkinsonism, cognitive impairment, and mood in smoking and nonsmoking patients with PD;
- in study 2 evaluated whether mental fatigue is a symptom that appears independently from other clinical features in patients with PD, and studied whether fatigue is a persistent complaint over time in these patients;
- in study 3 investigated various risk factors for and the rate of progression of motor symptoms and disability in a population-based cohort of patients with PD;
- in study 4 investigated how changes in motor subtype influence the risk for incident dementia in patients with PD.

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## 3 Methods

### 3.1 Patient selection and follow-up

Between September 1992 and May 1993, a population-based prevalence study was conducted in Rogaland county, Western Norway.<sup>16</sup> To achieve complete case ascertainment, an extensive search in hospital files was provided, and information from all relevant sources in the study area including general practitioners, nursing homes, district nurses, health workers and the Rogaland Parkinson's Disease Society was assessed. Of about 400 patients examined by neurologist with special interest in movement disorders, 245 patients were diagnosed with PD according to published diagnostic criteria.<sup>229</sup> The crude prevalence was 110.9 per 100,000 inhabitants and 102.4 per 100,000 after adjusting for age to a standard European population.

Of the 245 patients diagnosed with PD at baseline, 239 patients were able and wanted to participate in the study and constituted the patient cohort investigated in study 1. 233 patients of these were assessed for fatigue and included in study 2. The data of 232 patients with PD were available for analysis of risk factors and the rate of disease progression in study 3. Of these 232 patients, 171 were non-demented at baseline. These 171 patients were included in study 4. Patients were invited by letter to participate in follow-up examinations in 1997 and 2001. A total of 144 patients attended the first follow-up visit in 1997, and 89 patients were examined in 2001.

### 3.2 Control subjects (study 1)

Study 1 also used data from two control groups of same age and sex distribution as the PD cohort, examined in 1993. While one control group included 100 healthy and well-functioning elderly people derived from routine-visits at their general practitioners, the other consisted of 100 patients with another chronic disease

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(diabetes mellitus), selected randomly from the diabetes outpatient-clinic at the (former) Rogaland Central Hospital.

### 3.3 Diagnosis of PD

To achieve both high sensitivity and specificity in case ascertainment, a new diagnostic classification was used to diagnose clinical possible, probable, and definite PD.<sup>229</sup>

#### *I. Clinical definite idiopathic PD*

The patient presents resting tremor and at least two of the following signs: bradykinesia, rigidity, or postural abnormalities. In addition, unilateral onset and asymmetric development are mandatory, as well as good to excellent response to dopaminergic agents. Neither atypical signs or symptoms nor changes on computed tomography (CT) or magnetic resonance imaging (MRI) of the head are accepted.

#### *II. Clinical probable idiopathic PD*

Patients must fulfil at least two of four cardinal signs, but tremor at rest is not mandatory in this subgroup. A maximum of one the following atypical features may be present: (a) early mild dementia or clinically relevant autonomic failure, (b) symmetrical disease presentation, (c) only a moderate response to dopaminergic treatment, or (d) other atypical signs or symptoms indicating another parkinsonian disorder.

#### *III. Clinical possible idiopathic PD*

The patient must present at least two of the four cardinal signs. In addition, response to dopaminergic agents should be at least moderate. Mild to moderate dementia and autonomic disturbances may be allowed. A history indicating symptomatic parkinsonism due to drug treatment will lead to exclusion from this category.



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### 3.4 Assessment of parkinsonism and disability

All patients were examined by neurologists experienced in diagnostics and treatment of movement disorders. The same standardized examination program was applied at all study visits, including the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr staging, and the Schwab and England scale. These measurement instruments of motor function and disability are described in detail in section 1.8 "Assessment of disease severity and progression in PD".

In study 2 to 4, the disease subtype of the individual patient was classified as tremor-dominant (TD), indeterminate, or postural-instability gait difficulty (PIGD),<sup>102</sup> based on predominant motor symptoms in the UPDRS ADL and motor subscore: total tremor score was calculated as the mean tremor score in UPDRS subscale II and rest tremor score for face, upper and lower limbs, and postural or action tremor of both hands in UPDRS subscale III. Total PIGD-score was defined as the mean of the items falling, freezing, walking difficulties in UPDRS II, and gait and postural instability scores in UPDRS III. Disease subtype was classified as PIGD when the ratio of total tremor score/total PIGD score was equal to or less than 1.0, whereas patients with a ratio of 1.5 or more were defined to have TD subtype. When the tremor/PIGD ratio was more than 1.0 and less than 1.5 patients were classified to be in the indeterminate category.

### 3.5 Assessment of smoking habits (study 1)

Information on smoking habits was collected at baseline from all patients with PD and two control groups of healthy elderly and patients with diabetes mellitus. Those who did not smoke in 1993 were categorized as smokers. For smokers, pack-years were calculated by dividing the average number of cigarettes smoked per day in a given time interval by 20 and multiplying by the number of years smoked. To detect a possible dose relationship between smoking and progression of PD, smokers were

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classified into two groups based on the intensity of smoking: mild to moderate (<20 pack-years) and heavy smokers (20 pack-years and more).

### 3.6 Assessment of cognitive impairment and dementia

At baseline, all patients were assessed with the Mini-Mental State Examination (MMSE),<sup>84</sup> and a structured interview based on the DSM-III-R criteria was performed with their caregivers.<sup>230</sup> The Gottfries, Bråne & Steen Dementia scale (GBS)<sup>231</sup> was completed based on the clinical interview and examination.

A more extensive cognitive assessment battery was performed at follow-up visits. The Dementia Rating Scale (DRS)<sup>86</sup> was administered, and patients with a MMSE score of 16 or above completed a neuropsychological test battery including tests assessing visual memory (Benton Visual Retention Test),<sup>232</sup> executive functioning/attention (Stroop test),<sup>233</sup> and visuospatial functioning (Benton Judgement of Line Orientation Test).<sup>234</sup> For MMSE and DRS, age- and education-based cut-off scores were used. Dementia was diagnosed by two of the authors after reviewing all the available material, according to DSM-III-R criteria, and based on clinical interview, cognitive rating scales, and neuropsychological tests. The assessment of symptoms of cognitive dysfunction and dementia was performed blind to the motor evaluation.

### 3.7 Assessment of fatigue (study 2 and 3)

At all study visits, information from two different rating scales of patient-perceived fatigue was used to evaluate fatigue. First, lack of energy is rated as one of six dimensions in the Nottingham Health Profile (NHP), a health-related quality of life questionnaire, which has been extensively tested for validity and reliability.<sup>235</sup> NHP-items that were included in the evaluation of fatigue were “I am tired all the time”, “Everything is an effort”, and “I soon run out of energy”. In addition, all patients were asked to give a evaluation of feeling energetic or fatigued on a 7-point rating

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scale.<sup>154</sup> They were asked if they mostly felt very strong and healthy (1), strong and healthy (2), somewhat strong and healthy (3), cannot decide (4), somewhat tired and worn out (5), tired and worn out (6), or very tired or worn out (7). Patients who reported lack of energy in at least one of three questions on the NHP and scored four or more on the seven-point scale were classified as having fatigue.

To evaluate the validity of this classification, the Fatigue Severity Scale (FSS)<sup>88</sup> was added to the evaluation program in 2001. Mean FSS score for patients with PD suffering from fatigue according to our classification was 5.3 (SD 1.5) versus FSS score of 3.7 (SD 1.6) for patients without fatigue. This difference was highly significant ( $p < 0.001$ ).

### 3.8 Assessment of other non-motor symptoms

Severity of depressive symptoms was assessed using the Montgomery and Aasberg Rating Scale (MADRS)<sup>236</sup> and the Beck Depression Inventory (BDI).<sup>237</sup> While the first instrument is an examiner-rated assessment tool, the latter measures the level of patient-perceived depression. Both rating scales have been shown to be reliable, sensitive, and valid measurement instruments of depression.

At all study visits, patients also completed a questionnaire covering both daytime and nighttime sleep problems, including excessive daytime sleepiness, insomnia, and parasomnia-suspect features such as RBD and PLMS. In 2001, patients were also assessed by the Epworth Sleepiness Scale (ESS),<sup>238</sup> a validated and widely used assessment tool of daytime somnolence.

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### 3.9 Statistical analysis

In study 1, the progression of disease was measured as change in severity of motor impairment, disability, mood, and cognitive impairment between baseline examination and follow-up visits. Differences in means of changes in symptoms between smokers and non-smokers were compared by Students t-test and differences in proportions for categorical variables by  $\chi^2$  tests. For smoking and non-smoking PD patients, survival curves were calculated by the Kaplan-Meier method. A Cox regression model including adjustment for age in three categories (less than 70 years, 71-80 years, more than 81 years) and gender was used to calculate the relative risk for mortality in the two PD groups.

In study 2 to 4, Mann-Whitney tests and  $\chi^2$  tests were performed to compare medians and proportions between groups in cross-sectional data. When more than two groups were compared, Kruskal-Wallis tests and linear-by-linear association tests were used, and Mann-Whitney posthoc tests were performed when the overall test was significant. For longitudinal data, we performed logistic regression models for correlated data<sup>239</sup> to analyse the relationship between dependent and independent variables in studies 2 to 4, and to estimate the rate of functional decline over time in study 3.

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## 4 Results

### Study 1

We found a 50% higher prevalence of smokers among healthy elderly and patients with diabetes mellitus compared to a population-based cohort of patients with PD. In contrast, during the follow-up period, there were no significant differences in progression of parkinsonism, disability, cognitive impairment, and mood in smoking and nonsmoking patients with PD. Mortality was also similar in the two groups.

### Study 2

In PD patients who were followed throughout an 8-year study period, fatigue increased from 35.7% in 1993 to 42.9% in 1997 and 55.7% in 2001. Fatigue was related to disease progression, depression, and excessive daytime sleepiness (EDS). However, the prevalence of fatigue in patients without depression and EDS remained high and increased from 32.1% to 38.9% during the study period. For about 44% of the patients with fatigue the presence of this symptom varied during the study period, as it was persistent in 56% of the patients with fatigue.

### Study 3

Over the 8-year study period, we found a similar mean annual decline in the UPDRS motor score and the Hoehn and Yahr staging of 3.1% and 3.2%, respectively. Also the UPDRS Activity of Daily Living score and the Schwab and England scale changed similarly, with 3.5% and 3.6% per year, respectively. Age, age at onset, disease duration, and excessive daytime somnolence at baseline were strong and independent predictors of greater impairment in motor function and disability. Cognitive impairment at baseline predicted higher disability and higher Hoehn and

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Yahr staging. Time by age-at-onset interactions were found for the UPDRS motor score and the Hoehn and Yahr staging.

#### **Study 4**

Transition from tremor-dominant (TD) to postural instability gait difficulty (PIGD) subtype was associated with a more than 3-fold increase in the rate of MMSE decline. Compared to patients with persistent TD or indeterminate subtype, the odds ratio for dementia was 56.7 (95% CI 4.0-808.4;  $p=0.003$ ) for patients changing from TD or indeterminate subtype to PIGD subtype, and 80.0 (95% CI 4.6-1400.1;  $p=0.003$ ) for patients with persistent PIGD subtype. Patients with TD subtype at baseline did not become demented until they developed PIGD subtype, and dementia did not occur among patients with persistent TD subtype of parkinsonism.

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## 5 Discussion

### 5.1 General aspects of methodology

The primary goal of epidemiological research is to provide information on the development, prevalence and progression of diseases, and their associated risk factors in the general population. Interpretation of data from epidemiological research is thus the basis of increasing our understanding on the etiology of diseases and in consequence the starting point for identifying at risk-groups in the population, prevention of diseases, development of treatment strategies, and health care planning. Because epidemiological data, by definition, refer to the general population and reflect characteristics of a representative sample of individuals suffering from a given disease, quality of epidemiological research highly depends on diagnostic accuracy and completeness of case-ascertainment.

In PD, the diagnosis during lifetime is still based on disease history and clinical examination, as no biomarkers are currently available to prove the clinical diagnosis. Therefore, and because PD is characterized by clinical heterogeneity and symptoms may overlap with those of other conditions such as atypical parkinsonian disorders and symptomatic parkinsonism, use of careful diagnostic criteria is essential to provide valid information on the disease. One of the major challenges in PD research is to achieve high diagnostic specificity and sensitivity, that is, to include all patients with the disease while excluding those not suffering from PD. Diagnostic accuracy has particular importance when measuring disease progression in PD. For example, inclusion of patients with essential tremor, that is frequently reported to have been diagnosed as PD, would lead to an overestimate of the prevalence of the disease, but underestimate of the rate of disease progression. In contrast, inclusion of subjects suffering from atypical parkinsonian disorders, characterized by rather rapid functional decline, would tend to give a worse impression of both the frequency and course of the disease.

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Several autopsy studies from the early 1990s reported poor accuracy in clinical diagnosis of PD, with pathological evidence of PD in not more than 76%, even when patients were diagnosed by neurologists.<sup>240, 241</sup> As a consequence, we applied a new diagnostic classification in our studies to diagnose patients with PD at different levels of confidence to achieve both high sensitivity and specificity.<sup>229</sup> In addition, our longitudinal design including re-evaluations after four and eight years made it possible to revise the clinical diagnosis in patients who had developed signs and symptoms atypical in PD. Of the 245 patients included at baseline, less than 3% were rediagnosed as not suffering from PD during follow-up, and of those who underwent autopsy (22 patients), all fulfilled neuropathological criteria of PD.<sup>242</sup> For the sake of comparison, in a clinicopathological study from the United Kingdom, the positive predictive value of the clinical diagnosis of idiopathic PD provided by movement disorders specialists according to the UK Brain Bank criteria was 98.6%, while sensitivity was 91.1%.<sup>243</sup>

In addition to achieve high diagnostic specificity and sensitivity, we made great efforts to include all patients within the study area. An unfavorable trend of case-ascertainment in many studies is to include patients based on retrospective review of medical records. Such clinic-based data are likely to reflect information from highly selected subpopulations with more advanced or more complicated disease, but in which the study subjects are still mobile and able to visit the hospital or outpatient-clinic. Thus, patients not referred to the outpatient clinic, particularly those living in institutions, are likely to be underrepresented in such surveys. Several lines of evidence support that nursing home placement leads to underrecognition and -diagnosis of patients with PD.<sup>244, 245</sup> About 5% of residents in Norwegian nursing homes were found to have clinical PD, 18% of whom were previously undiagnosed.<sup>244</sup> Therefore, in addition to search in hospital files, case-ascertainment in our study was based also on information from the Rogaland Parkinson's Disease Society, all general practitioners, health workers, district nurses, and nursing homes in the study area. Some subjects within the study area, for example those with very early and undiagnosed disease, may still have been missed, as indicated by generally



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higher prevalence rates of PD in door-to-door surveys.<sup>17</sup> We are, however, convinced that our approach of patient selection was the best possible and available for our purpose, and that near all patients within the study area suffering from PD at prevalence day on January 1<sup>st</sup>, 1993, were included. Of note, due to a stable patient population and only few patients withdrawing their consent in participation, loss to follow-up for these reasons was very low. However, a concern in our study design was the rather long time intervals between study visits, resulting in a high attrition rate and potentially confounding due to death.

Another important issue in epidemiological research is the use of appropriate measurement instruments. We performed standardized assessment of our patients at each study visit and applied generally accepted and validated measurement instruments. These are thoroughly described in the first and third part of this thesis. However, because of lack of validated tools for assessment of some non-motor features in PD at study start, self-constructed questionnaires or combined information from different scales had to be used to assess the frequency and severity of some of these symptoms. We attempted to solve this problem of uncertain validity by including later developed and validated measurement instruments and by comparing their results with those derived from our self-constructed tools, as it was done for FSS and ESS. The fact that our classifications of fatigue and EDS correlated with these widely used and acknowledged assessment tools therefore was an important observation and strengthened our findings on these features. Adding the FSS and ESS was undoubtedly also helpful to make our results better comparable with those of later published studies on fatigue and EDS in patients with PD.

Last but not least, the application of adequate statistical methods is an important methodological aspect. However, particularly longitudinal studies using multiple observations over time may be a challenge to the researcher and statistician, as usual statistical techniques for analysis of longitudinal data are not applicable. In study 1, we measured disease progression by comparing mean changes in severity of symptoms from baseline to the first and second follow-up visit in smokers and non-

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smokers, thus following a statistical approach similar to those chosen in several clinical PD trials.<sup>208, 246</sup> In study 2 to 4, we used logistic regression models for correlated data. These account for multiple visits per individual and the fact that characteristics of a single subject over time are likely to correlate with each other.<sup>239</sup> They allow quantifying the difference in scores at each study visit between patients who have a given factor at baseline versus those who have not. Logistic regression for correlated data accounts for missing data and allows including categorical and continuous variables in one model.

## 5.2 Risk factors and the rate of disease progression in PD

The role of genetic and environmental factors in the pathogenesis of PD has been the focus of research and debate over several decades. Since the first reports on the inverse relationship between smoking and PD were published almost fifty years ago, numerous studies have suggested a biological protection by cigarette smoking against nigral neuronal degeneration. In a recent systematic review of prospective studies, the pooled risk estimate between ever smokers and PD was about 0.5, meaning that those ever having smoked are half as likely to develop PD compared to never-smokers.<sup>247</sup> Surprisingly, during the same period only one study, following 30 patients over 3 years, investigated the influence of cigarette smoking on disease progression in PD and found no difference between smokers and non-smokers. As we hypothesized that cigarette smoking, if significantly neuroprotective, would slow down functional decline in patients already diagnosed with PD, we measured in study 1 changes in severity of parkinsonism, disability, cognitive impairment and mood over an eight year period in smoking and non-smoking patients with the disease. We also compared the prevalence rate of smokers among PD patients and control groups with similar age and sex distribution. In these groups consisting of healthy elderly and patients with diabetes mellitus, we found a 50% higher prevalence of smokers than in patients with PD, which is in line with previous studies.<sup>247</sup> This was an important finding as it indicated that smoking habits in our PD population were in principal not different

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from those of previously investigated cohorts. However, progression of motor impairment, disability, mood, and cognitive impairment was not different in smokers and non-smokers. Of importance, this finding was not confounded or biased by selective mortality in the group of smoking patients as has been suggested previously to potentially explain the inverse relationship between smoking and PD.<sup>248</sup>

What may explain our findings of a lower prevalence of smokers in PD, but similar disease progression in nonsmoking and smoking patients with the disease?

We can not exclude that we have failed to detect less rapid disease progression in smoking patients due to methodological weaknesses in our study design. The rather small sample sizes at the last follow-up visit limited the statistical power, and thus differences in progression between the groups may have been missed. Therefore, we regarded the change in clinical features during the first four years of follow-up as the primary outcome. Also the fact that smoking habits were not updated at follow-up may have biased our results. Although we are unaware of any non-smokers starting smoking during follow-up, some patients may have quit smoking during the study period. We neither considered the possible influence of other substances such as coffee and alcohol on disease progression. However, based on the assumption that these are related to cigarette smoking and are suggested to have synergistic effects in protecting against nigrostriatal damage, one would expect a more pronounced rather than less difference in disease progression. Nevertheless, incorporation of these data would unlikely have changed our results substantially, as changes in severity of all assessed features were highly insignificant during both the first four and the entire eight years of follow-up. In a comment on our paper, Papapetropoulos and coworkers confirmed our findings and reported no difference in clinical characteristics of smokers, nonsmokers and past smokers in 127 deceased patients with pathologically confirmed diagnosis of PD, except for age at death. These results and their observation of younger age at disease onset in smokers than nonsmokers are in agreement with our and other<sup>52, 249</sup> findings and seem to contradict that cigarette

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smoking, as a single factor, has clinically significant neuroprotective effect in patients already diagnosed with PD.

Interestingly, in several studies,<sup>52, 250, 251</sup> but not all,<sup>252</sup> the inverse relationship between smoking and PD was present only or most pronounced in patients with early onset of PD in which genetic factors are more likely to be involved in the pathogenesis of the disease. In line with this, results from a recent well-designed Swedish case-control study using both co-twin and unrelated controls indicate that the association between smoking and PD to some extent is due to familial or genetic confounding.<sup>253</sup> Interactions between cigarette smoking and genes involved in familial PD, oxidative stress, and detoxification of metabolites have been suggested to modify the relationship between smoking and PD,<sup>53-55</sup> but could not be confirmed in larger studies or remain to be replicated.<sup>254</sup>

Another possible explanation is that patients with PD may be less prone to start smoking, and thus failure to develop strong smoking habits may be the first manifestation of the disease. Also, patients with PD may be more likely to quit smoking before clinical disease onset. In a recently published study investigating the relationship between life-style risk factors and personality traits in PD, patients stopped smoking in average 16.2 years prior to the onset of motor symptoms.<sup>255</sup> In this sense, the causation between smoking and PD would be reversed, and PD would „protect against smoking“. <sup>256</sup> A premorbid parkinsonian personality trait has been suggested in several studies.<sup>49</sup> Patients with PD are described as passiv, self-controlled, introverted, and less likely to take risks. Studies indicate that PD patients score lower than controls on a personality trait called novelty seeking which is hypothesized to be dopamine driven.<sup>51</sup> Dopamine is likely to play an important role in pleasure and reward systems, as also indicated by reports of levodopa addiction and personality changes in PD patients with dopamine dysregulation syndrome.<sup>257</sup> Moreover, a recent study found that low sensation seeking independently predicts PD after adjusting for smoking, caffeine and alcohol intake.<sup>255</sup> However, in a nested case-control study, the inverse association between smoking and PD was present even in

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PD patients with the highest scores for depression and social introversion, assessed decades before clinical onset.<sup>258</sup> The latter observation would argue against a reverse causation hypothesis, but has still not been published in detail and should therefore be interpreted with caution. Identification and prospective neuropsychological studies of subjects with preclinical PD seem now to be within reach and would be able to provide valuable information whether and to which extent a premorbid parkinsonian personality traits could explain the comparatively low prevalence of smokers among PD patients.

In a more comprehensive survey (study 3), we prospectively assessed potential demographic and clinical risk factors and the rate of functional decline in our PD cohort. Although a number of studies had investigated predictors of disease progression in PD prior to our study, most of them were potentially biased by methodological weaknesses, including short follow-up, small sample size, selected patient cohorts and retrospective design. Not surprisingly, their results were contradictory on many potential risk factors and varying regarding the rate of disease progression.<sup>122</sup>

Because predictors and the rate of functional decline may vary depending on what kind of assessment tool is used, we decided to measure the progression of motor impairment and disability each independently by two different assessment tools, all of whom are widely used and acknowledged by PD researchers. Our observation of similar annual changes in severity of motor symptoms and disability in between 3.1% and 3.6% measured by four different measurement instruments was valuable not only from a clinicometric point of view. They also indicated that the rate of motor progression, as derived by long-term follow-up of an unselected patient cohort, is at least twice as high as reported previously from other prospective longitudinal investigations.<sup>116</sup> Interestingly, Louis and colleagues investigated motor progression in a population-based cohort with almost identical sample size, gender distribution, age at onset, and age at baseline, but with shorter disease duration and follow-up compared to our study, and found only a 1.5% annual decline in UPDRS motor

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score.<sup>116</sup> Jankovic et al. reported a 0.7% motor progression in their study with similar follow-up compared to our, but using a selected cohort of patients with rather young age at onset.<sup>117</sup> These differences in progression rates and the fact that both studies failed to identify independent risk factors of motor decline illustrate that rather small methodological varieties in longitudinal studies in PD may have major impact on their outcome.

An important part of this study was to explore the relative importance of different baseline variables for future functional decline. We therefore conducted logistic regression analysis for correlated data and included a wide range of clinical and demographic features as independent variables. By testing each independent variable for interaction with follow-up time it is possible to judge whether this variable is associated with more rapid progression of the dependent variable. From an etiological point of view it was of interest to explore the importance of both the patients' age at onset and their age at baseline in addition to disease duration, because they are likely to reflect different pathogenic mechanisms. As these variables could not be assessed in one model due to collinearity, we performed two analyses in which age at onset and disease duration were included in the main model, and age at onset and age at baseline in a supplemental analysis.

We found that the presence of non-motor symptoms thought to be due to non-dopaminergic pathology, such as cognitive impairment and EDS, predicts a poor outcome in the sense of more impaired motor function and disability. We believe that these conditions in general reflect more advanced and widespread disease, in which also typical motor symptoms become less responsive to dopaminergic stimulation, possibly due to degeneration in postsynaptic dopaminergic terminals. Also a higher age at baseline and longer disease duration predicted higher levels of functional impairment during follow-up, but none of these features did interact significant with time. Thus, we could not confirm the results from a recent neuroimaging study suggesting that the rate of progression may decrease in a negative exponential manner.<sup>72</sup> In fact, we consider this to be one of the major findings of our study, as it

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highlighted the current limitations of neuroimaging studies to reflect clinical long-term disease progression in PD by measuring dopamine transporter activity or metabolism.

We found time interactions only for the patient's age at onset, however, both for the UPDRS motor scale and the Hoehn and Yahr staging, which clearly strengthens the significance of this finding. Advanced age at onset but not higher age per se therefore appears to be the major predictor of motor decline in PD, as indicated by previous studies, suggesting that PD is not due to an accelerated aging process.<sup>102, 120</sup> For example, we estimated the rate of motor decline measured by the UPDRS motor scale to be about 1.5 more rapid in patients with disease onset at 70 years compared to those with onset at an age of 50 years, and almost twice as rapid using the Hoehn and Yahr staging. Our statistical method also allowed to estimate the time for progressing one Hoehn and Yahr stage, which was 5.1 year for patients with disease onset at 70 years and 9.3 years for those who were diagnosed with PD at an age of 50 years. To our knowledge, we were the first to present age at onset-dependent estimates on progression rates derived from long-term follow of a representative PD cohort. It is, however, important to note that our estimates were derived from drug-treated patients in their on-stage, and that the natural progression of the disease is likely to be more rapid, at least in patients with early disease. In contrast, our results provide more true-to-life estimates on functional decline and may be particularly relevant for long-term investigations of symptomatic or potentially neuroprotective agents in PD.

## 5.3 Fatigue within the non-motor symptom complex of PD

Although fatigue is one of the most frequent and disabling non-motor features in PD, described as their most disabling symptom by one-third of patients with the disease, it is under-recognised by clinicians as well as researchers. Basically, fatigue is a highly physiological phenomenon, describing tiredness, weariness, exhaustion or drain of

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energy, and a normal feedback of perceived exertion. However, in research terms it is best understood as a pathologically amplified reaction to mental or physical tasks. A now widely accepted and used definition of fatigue is "an overwhelming sense of tiredness, lack of energy, or feeling of exhaustion".<sup>259</sup>

Fatigue is not specific to any disorder in the sense that it is common in several neurologic, psychiatric, and systemic diseases.<sup>143, 260, 261</sup> Suggested underlying pathways depend on the type of disorders, and include abnormal immune response, alterations in neurotransmitter signaling, and genetic predisposition, among others.

Our study (study 2) was the first to investigate fatigue prospectively over time in a community-based cohort of PD and was primarily motivated by a previous report of persistence of fatigue in a small sample of retrospectively assessed patients with PD.<sup>156</sup> In addition, we aimed to clarify to which extent the relationship to other motor and non-motor features could explain the prevalence of fatigue, as previous prevalence studies had shown inconsistent results.<sup>145</sup> In general, persistence and increase of prevalence over time indicate a symptom to be caused by structural lesions rather than due to confounding by comorbidity or overlap with other features.

Methodological challenges in assessing fatigue in PD include the lack of objective measurement instruments, the overlap of symptomatology with other non-motor problems, and the fact that it is not specific to the disease. In addition, fatigue may have different dimensions, and we therefore specified that we aimed to investigate aspects of mental fatigue. Because it is highly subjective, the most appropriate way to assess fatigue is to measure the patient's own perception of this complaint by self-report. We used combined information from a seven-point fatigue rating scale and from parts of the energy-dimension in the Nottingham Health Profile to measure fatigue and extended our evaluation program in 2001 by the FSS which meanwhile had become an acknowledged and widely used assessment tool. However, although these assessment tools were designed to measure fatigue, none of them are specific to this complaint. To address the known problem of potential overlap and comorbidity



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between fatigue and other PD features, we did a comprehensive assessment of other non-motor features and carried out multivariate analysis to identify covariates that were significantly related to fatigue. We then calculated prevalence rates of fatigue at each study visit for two different populations: first, for all included patients; and second, for a subgroup of patients defined by low levels of covariates associated with fatigue.

Our results confirmed previous findings of a high frequency of fatigue in PD, affecting slightly less than 40% at baseline and more than 56% after eight years of follow-up. We further found that fatigue was related to other non-motor symptoms like EDS and depression, both of which are thought to originate from pathological changes outside the classical pathway of substantia nigra. Unfortunately, because of low specificity of current evaluation instruments, it remains unclear whether this association is causal or due to overlap of symptomatology. However, several observations in our study imply that fatigue cannot be explained by comorbidity alone: First, fatigue occurred as a frequent complaint also in patients without these symptoms; second, it increased in prevalence during follow-up; and third, fatigue was independently associated with the Hoehn and Yahr staging. Taken together, these findings strongly suggest that fatigue is caused by disease-related changes in a substantial part of patients with PD.

Another aim of this study was to clarify whether fatigue is a persistent feature in patients with PD. We did not expect strict persistence of fatigue in our patients, again because of its in general multifactorial etiology and due to potential overlap and comorbidity with other symptoms in PD. In line with our expectations, but in contrast to the study by Friedman et al., fatigue occurred as a non-persistent symptom in almost half of those patients who participated in all study examinations. Our results therefore demonstrate that the symptomatology of fatigue in PD and its underlying causes are likely to be heterogeneous, and they also highlight the complex interactions between different non-motor symptoms in PD. In about half of the patients fatigue seems to be related to the disease pathology itself, and in the other

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patients it may be explained by comorbidity or overlap with other non-motor problems, particularly depressive symptoms and EDS. This clearly contrasts the conclusion of a recently published review article, describing fatigue as a symptom that is unrelated to motor severity and sleep disturbances in patients with PD.<sup>145</sup>

Our results have implications for clinical practice and future research on fatigue in PD: First, because fatigue is a frequent and increasing complaint it should be assessed regularly in routine examination of patients with PD. Second, in those suffering from fatigue, a thorough examination of other motor and non-motor symptoms should be conducted in parallel to elucidate if fatigue may be explained by these. If a relationship to other symptoms is likely and these are treatable, their treatment also may diminish the patient's experience of fatigue. Third, future studies on fatigue should take into account the heterogeneity of fatigue in PD. For example, to obtain valid results in clinicobiological correlation studies, case ascertainment should preferentially concentrate on patients without overlapping symptomatology, as disease-related changes are most likely to explain fatigue in these subjects.

## 5.4 Changes in motor subtype and risk for incident dementia in PD

It is now established that cognitive impairment and dementia are common features in PD, developing in the vast majority of patients and predicting nursing home placement and mortality.<sup>134, 136, 173</sup> Thus, cognitive decline in PD has major consequences for the patients themselves, their caregivers, and the health care system. It is therefore important to clarify which factors may predict future development of dementia. In addition, establishing associations between different symptom complexes within PD may contribute to increase our understanding of underlying pathological changes.

The existence of clinical subtypes in PD has been suggested for several decades, based on differences in patterns of motor symptoms and their influence on cognitive

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and functional decline. Later on, results from cerebrospinal fluid analysis in PD supported the concept of different motor subtypes in PD.<sup>262</sup> Zetuský et al. were among the first to distinguish between a tremor-dominant (TD) subtype and motor impairment characterized by postural instability and gait difficulties (PIGD), and pointed out that TD parkinsonism is associated with relative preservation of mental functioning.<sup>263</sup> In contrast, motor impairment characterized by postural instability and gait difficulties (PIGD) correlated with cognitive impairment in cross-sectional studies and predicted dementia in the only longitudinal investigation published prior to our study.<sup>141</sup> Because both conditions are more or less refractory to dopaminergic treatment, underlying non-dopaminergic pathology has been suggested.<sup>264</sup>

However, several issues regarding the relationship between these symptoms remained unclear or were not addressed in previous studies. For example, based on our clinical experience, we expected the motor subtypes to change over time, at least in some of our patients. This was important to consider in our study design (study 4). We also wondered whether eventual changes in predominant motor symptoms were associated with increased risk for becoming demented. Therefore, instead of assessing risk factors at baseline, we investigated how changes in motor subtypes during the study period influenced the development of both cognitive impairment and dementia in the subgroup of all 171 patients who were non-demented at baseline. This approach was also suitable to test clinically the proposal of a sequential development of disease pathology in PD as supposed by Braak et al.<sup>75, 76</sup> Their hypothesis was met with scepticism when published in 2003, because it was based on cross-sectional data and suggested rather unexpectedly that the disease process begins in lower brainstem areas (vagus and olfactory nerve), remaining subclinical until substantia nigra is affected. While several clinical studies, particularly those investigating olfactory function, have provided clinical support to a stagewise progression of PD pathology in subclinical and early PD,<sup>202</sup> we were unaware of any studies supporting Braak's proposal in advanced disease. Based on the assumption that brainstem and midbrain locomotor areas (Braak stage 3 and 4) are crucial for control of balance and gait,

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while cortical deficits (stage 5 and 6) best relate to dementia in PD, one would expect a sequential development of these symptoms in patients with PD.

We found that a considerable portion of our patients changed their motor subtype during the eight years of follow-up. In this context, an important observation was that these changes in motor subtype were not random, but clearly unidirectional from early TD parkinsonism via the indeterminate to the PIGD motor subtype. This finding confirmed the proposal that motor subtypes may differentiate or evolve during the course of the disease, as suggested previously based on cross-sectional data and CSF analysis in patients with PD.<sup>102, 262</sup> Compared to 54% at baseline, 88% of our patients had developed clinically significant and irreversible postural instability and gait problems at study end, despite dopaminergic treatment, which implies underlying cerebral changes involving non-dopaminergic pathology. This is identical to the 88 % prevalence of PIGD motor subtype in patients with PDD reported previously.<sup>264</sup>

Our data further suggest that a minority of patients remains with a tremor-dominant disease pattern, and that these patients are “protected” against cognitive decline and development of dementia. Patients with persistent TD parkinsonism showed a total MMSE decline of only 1.2 points during eight years, compared to an expected decline in MMSE of one point per year in the general PD population.<sup>132</sup> One could argue that these patients may not suffer from PD but another disease, for example essential tremor which is frequently misdiagnosed as PD and associated with preserved cognitive function. However, although we have no confirmation of the clinical diagnosis by autopsy in these patients, they all fulfilled criteria of PD at each study visit, presenting at least one additional cardinal feature in addition to resting tremor and most of them a asymmetric disease pattern. Interestingly, a very recent study supports these finding and suggests the existence of a subgroup of patients with PD suffering from “benign tremulous parkinsonism”.<sup>265</sup> The clinical features and longitudinal course in these patients, including preserved cognitive function and rather poor levodopa responsiveness of tremor, were strikingly similar to those observed in our patients with persistent TD subtype. Neuroimaging studies in patients

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with this phenotype further demonstrate reduced striatal dopaminergic uptake, as expected in PD but not in tremor syndromes.<sup>266</sup> We speculated that disease pathology in patients with persistent TD parkinsonism may progress differently and for some reason remains more restricted than in patients developing indeterminate or PIGD motor subtype.

Somewhat unexpectedly, we observed a strict sequential development of PIGD motor subtype and dementia in our cohort in the sense that, except for one, no patient was diagnosed with dementia before transition to PIGD parkinsonism. It was therefore not surprising that we found very high odds ratios for dementia for those who had or developed PIGD subtype compared to patients with stable TD or indeterminate motor subtype. However, the intervals between study visits were rather long, and some patients with TD or indeterminate subtype might have been found to be demented using more frequent study visits. In a previously published prevalence study, 5% of demented patients presented with TD parkinsonism.<sup>264</sup> We therefore also investigated the relationship between motor subtype and dementia diagnosis in the primarily excluded patients with dementia at baseline and found again that all but one of these suffered from clinically significant gait and balance problems. This observation clearly strengthened our primary findings in non-demented PD patients.

An important step to further clarify the relationship between PIGD and cognitive decline was to additionally investigate the rate of MMSE decline before and after changes in subtype of parkinsonism, because the MMSE score is a more sensitive method to detect minor or beginning cognitive impairment and thus better reflects the slowly progressive cognitive decline in patients with PD. Our finding of a more than threefold accelerated rate of MMSE-decline in those evolving from TD to PIGD parkinsonism strongly suggests that the cognitive decline in patients with PD starts in parallel to the development of clinically significant gait and balance problems. This also explains our observation of a subsequent diagnosis of dementia.

At the time of submission of our study there was convincing evidence for an involvement of the pedunculo pontine nucleus (PPN) in control of postural instability

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and gait problems, however, based on results from animal studies only.<sup>109</sup> Very recently, two independent preliminary investigations reported marked improvement of akinesia and postural instability by deep brain stimulation (DBS) of the PPN in patients with PD.<sup>267, 268</sup> It is therefore reasonable to relate the development of PIGD motor subtype in our cohort to functional or structural changes in the PPN or vicinal brainstem nuclei. Our findings on the strong temporal relationship between development of gait and balance problems on one hand and cognitive impairment on the other thus suggest that brainstem pathology is involved in the pathogenesis of (early) cognitive impairment in PD. Previous and more recent neuropathological studies, among these an autopsy study in a subgroup of our own cohort, support this assumption.<sup>76, 242</sup> In addition, our results may indicate that Braak's proposal of a sequential development of PD pathology is true also in advanced disease. However, whether and to which extent the PPN is directly or indirectly involved in the etiology of cognitive decline in PD remains unclear. Our study group plans to further investigate this issue in clinicopathological correlation studies of patients derived from our own cohort.

Finally, our findings suggest that the frequency and extent of cognitive assessments in patients with PD may be adjusted to their expected risk to become demented. Because patients developing clinically significant gait and balance problems are at 50% risk for dementia within the following four years, more frequent clinical follow-up in these subjects may lead to early detection and treatment of their cognitive deficits.

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## 6 Conclusions

The aims of this thesis were to describe and achieve a better understanding of aspects related to the clinical disease progression in Parkinson's disease (PD). All studies were conducted in a population-based cohort of patients with PD followed prospectively over an eight-year period.

The etiology and relative importance of genetic and environmental factors for the development and progression of PD are widely unknown. Lifestyle factors including cigarette smoking have been suggested to modify the course of the disease. In an exploratory study, we therefore investigated the relationship between cigarette smoking and PD. We confirmed previous findings of an inverse relationship between smoking and prevalent PD, but found no differences in progression of parkinsonism, disability, mood, and cognitive impairment during eight years of follow-up. Our results may indicate that smoking, as a single factor, does not have major neuroprotective effect in patients already diagnosed with PD.

In a more comprehensive study investigating clinical and demographic risk factors and the rate of functional decline, we show that motor symptoms and disability in PD progress with similar annual rates of 3.1% to 3.6%. This is in line with the general understanding of PD as a slowly progressive neurodegenerative disorder. However, the rate of functional decline varies between subgroups. Our data suggest that advanced age at onset is the major predictor of more rapid motor progression in patients with PD.

We further investigated different aspects of disease progression within the non-motor symptom complex of PD. We found that fatigue is a frequent and increasing complaint in PD. In about half of the patients it occurs as a fluctuating symptom and is related to other non-motor symptoms like depression and excessive daytime somnolence. However, fatigue appears independently from these symptoms in a substantial part of patients with PD and behaves like a symptom caused by

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malfunction or damage of relevant but so far unidentified brain areas.

Finally, we demonstrated that development of clinically significant postural instability and gait problems in PD is associated with a more than threefold accelerated cognitive decline and a 50% risk for becoming demented within the following four years. Our findings suggest common or parallel underlying pathological changes of gait and balance problems and cognitive impairment, and they also lend clinical support to Braak's hypothesis of a sequential development of pathological changes in PD.



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